

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

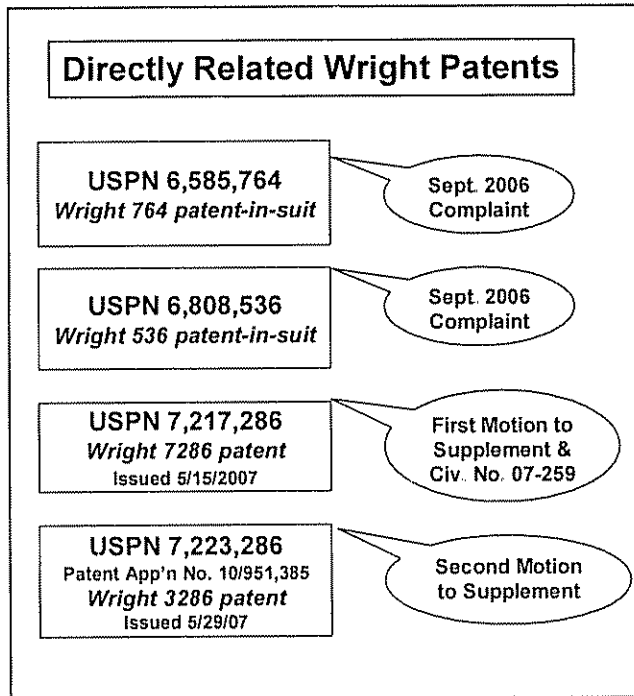
ABBOTT LABORATORIES and)	
ABBOTT CARDIOVASCULAR)	
SYSTEMS, INC.,)	
)	
Plaintiffs,)	
)	
v.)	C. A. No. 06-613-SLR
)	
JOHNSON AND JOHNSON, INC. and)	
CORDIS CORPORATION,)	
)	
Defendants.)	

**PLAINTIFFS' SUPPLEMENTAL MOTION FOR LEAVE TO FILE A
SUPPLEMENTAL COMPLAINT OR IN THE ALTERNATIVE TO
CONSOLIDATE RELATED ACTIONS**

Pursuant to Federal Rules of Civil Procedure 15 and 42, Plaintiffs Abbott Laboratories, Inc. and Abbott Cardiovascular Systems, Inc. (collectively, "Abbott") respectfully move for leave to file a supplemental complaint adding a claim for declaratory judgment of invalidity and noninfringement of United States Patent No. 7,223,286 ("*the Wright 3286 patent*"). *The Wright 3286 patent* issued from the Patent Office today and is directly related to the Wright patents at issue in Plaintiffs' original complaint (U.S. Patent Nos. 6,585,764 and 6,808,536) and U.S. Patent No. 7,217,286 ("*the Wright 7286 patent*"), which issued on May 15, 2007. With regard to all four Wright patents, Abbott alleges they are invalid and not infringed by Abbott's XIENCE V drug-eluting stent system.

The present motion is a supplement to a motion filed by Abbott on May 15, 2007 ("*the First Motion to Supplement*"). In the First Motion to Supplement, Abbott moved

(1) for leave to file a supplemental complaint adding a claim relating to the Wright 7286 patent, which issued on May 15, 2007, or (2) in the alternative, for the Court to consolidate this Civil Action with Civil Action No. 07-259-SLR (which is an independent declaratory action relating to the Wright 7286 patent).¹ (D.I. 43.) Abbott now simply seeks to add the newly-issued *Wright 3286 patent* to this case. The proposed supplemental Complaint and alternative proposed orders are attached as Exhibits 1 and Attachments A and B, respectively. In a nutshell, whether by supplementation or consolidation, Abbott is seeking to have this Court hear, as a single case, its declaratory judgment claims regarding four directly-related patents and one accused product.



DISCUSSION

In this declaratory judgment action, Abbott asserts, *inter alia*, that the Wright 764 and 536 patents-in-suit are invalid and not infringed by Abbott's XIENCE V drug-eluting

¹ Even though the Wright 7286 patent is in the Wright patent family, during prosecution, alleged inventor Wright was dropped as an inventor and Falotico was added. (See D.I. 48 at Ex. 11.) Thus, alleged inventor Falotico appears on the face of the Wright 7286 patent instead of Wright. For sake of clarity, this patent is referenced as the "Wright 7286 patent" because it is part of the Wright family of patents (even though Wright is no longer a named inventor). In the First Motion to Supplement, the Wright 7286 patent is referenced as the "Falotico 286 patent." Plaintiffs apologize for any confusion but believe that the current nomenclature will be clearer at the end of the day.

stent system. On May 15, 2007, Abbott moved for leave to file a supplemental complaint to assert a declaratory judgment claim relating to the recently-issued Wright 7286 patent, which is a continuation of the Wright 764 and 536 patents-in-suit. (D.I. 43.) In the First Motion to Supplement, Abbott also advised the Court that the Patent Office was about to issue another Wright patent from patent application no. 10/951,385 (“the Wright 385 application”), which is also related to the Wright 536 and 764 patents-in-suit and the Wright 7286 patent, and that Abbott would seek to add a declaratory judgment claim relating to that patent to this lawsuit. (D.I. 44 at 6, n.3.) Today, as Abbott advised, the Wright 385 application did in fact issue as *the Wright 3286 patent* and should be added to this case.²

Importantly, Abbott raised Defendants’ threatening actions, and the basis for this Court’s subject matter jurisdiction, with regard to the Wright 385 application (now the *Wright 3286 patent*) long ago in Abbott’s original September 2006 Complaint:

40. On August 7, 2006, J&J filed a “Petition to Make Special Because of Actual Infringement” (“Wright Petition”) with the United States Patent and Trademark Office in the matter of United States Application Serial No. 10/951,385 (“Wright ‘385 application”). The Wright ‘385 application is related to the Wright ‘764 and the Wright ‘536 patent. ...

41. In the Wright Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE™ V immediately upon issuance of the Wright ‘385 application as a patent. Among other things counsel for J&J asserted:

² Abbott notes that on May 23, 2007, the Patent Office mailed an Issue Notification for U.S. Application No. 11/466,983. (Ex. 4, Issue Notification.) This Wright patent is scheduled to issue on June 12, 2007. Like the Wright 7286 and the *Wright 3286 patents*, this application also claims priority to the Wright 764 and 536 patents-in-suit. (*Id.*, Priority Claim) In fact, it is a direct continuation of the *Wright 3286 patent*. (*Id.*) When this patent application issues into a patent, Abbott will promptly move to supplement its Complaint to add declaratory judgment claims of invalidity and noninfringement as to the patent issuing from that application.

Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch the XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of at least claims 103 and 130 on file in this application.

It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of at least claims 103 and 130 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

42. The subject matter of at least claim 103 of the Wright '385 application overlaps with subject matter claimed in the Wright '764 patent and the Wright '536 patent.

(D.I. 1, ¶¶ 40-43.) Defendants' "Petition To Make Special Because Of Actual Infringement" for the Wright 385 application (now the *Wright 3286 patent*), with the accompanying attorney declaration, was attached as Exhibit G to Abbott's September 2006 Complaint. (*Id.* at Ex. G.) Thus, the Wright 385 application has long been part of this case.

As of today, the Wright 385 application has issued as the *Wright 3286 patent*. As was expressly foretold in the First Motion to Supplement, Abbott now seeks to add a declaratory judgment claim concerning the newly-issued *Wright 3286 patent*. (D.I. 43 at 6, n.3.) The new version of the Supplemental and Amended Complaint is attached as

Exhibit 1 (with a redline against the original September 2006 complaint attached as Exhibit 2).³

As a matter of judicial economy and efficiency, the invalidity and noninfringement of these related Wright patents should all be tried as part of the same case. The *Wright 3286 patent* is a child of the Wright 536 and 764 patents-in-suit. (See Ex. 1 at Ex. D, Wright 7286 patent at cover.) The *Wright 3286 patent* is also the parent of the other newly-issued Wright 7286 patent. (*Id.*) In other words, all four patents have the same disclosure and specification. Thus, in construing the claims of any one of these four patents, the Court must not only consider this same disclosure and specification, but also must consider the file histories of all four patents. Moreover, the subject matter of the *Wright 3286 patent* is so closely related to the Wright patents-in-suit that, during the prosecution of the *Wright 3286 patent*, the Patent Office rejected the issued claims as “not patentably distinct” from claims of the Wright 764 patent-in-suit. (Ex. 3, Office Action and Terminal Disclaimers.) Defendants were forced to file “Terminal Disclaimers” to overcome the Examiner’s rejections. (*Id.*) In view of the interrelatedness of these patents, and the fact that there is only one accused product, it would promote the interests of judicial economy for one Court to consider these four patents together. (See D.I. 44 at 3-6.)

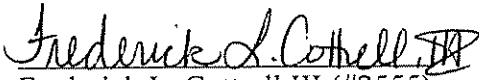

The relevant law relating to supplementing a complaint in view of newly-issued related patents is set forth in Abbott’s First Motion to Supplement. (D.I. 44 at 1-6, 9-12.)

³ The version of the Complaint attached as Exhibit 1 includes all the changes proposed in Abbott’s First Motion to Supplement and new Claim V, which is the declaratory judgment claim for the *Wright 3286 patent*. In addition, a few minor, non-substantive changes were made to clarify language and correct typographical errors in the first proposed supplemental complaint. (See, e.g., footnote 1, *supra*.)

For the reasons set forth in that motion, Defendants cannot show that adding the *Wright 3286 patent* to this case involving related Wright patents and the same accused product will cause undue prejudice or delay. To the contrary, Abbott's proposed supplementation will promote judicial efficiency and conserve judicial resources. Thus, for the reasons set forth above and for the reasons set forth in Abbott's First Motion to Supplement, Abbott respectfully requests that the Court grant Abbott's First Motion to Supplement and this second motion to supplement and allow Abbott to file the Complaint attached as Exhibit 1.⁴ Further, Abbott requests that the supplemental complaint be deemed filed *nunc pro tunc* as of the filing of Abbott's motions to supplement as set forth in the proposed order.

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*Attorneys for Plaintiffs Abbott
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Systems, Inc.*

Date: May 29, 2007

⁴ In the alternative, in the First Motion to Supplement, Abbott requested that the Court consolidate this case with Civil Action No. 07-259-SLR, which was filed on May 15, 2007 and is an independent action seeking a declaratory judgment on the Wright 7286 patent. (D.I. 44 at 6-12.) Abbott still seeks this alternative relief (*see* Attachment B) and will also be filing, concurrently herewith, a motion to supplement to add a claim relating to the now-issued *Wright 3286 patent* in that action. Abbott further notes that on May 15, 2007, Defendant Cordis filed a separate action against Plaintiff Abbott Laboratories in the District of New Jersey regarding the Wright 7286 patent. Abbott has, however, moved to enjoin the prosecution of that action. (*See* C.A. No. 06-613-SLR, D.I. 47, Motion to Enjoin; C.A. No. 07-259-SLR, D.I. 7, Motion to Enjoin.)

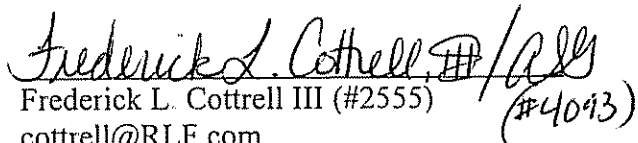
CERTIFICATE OF SERVICE

I hereby certify that on May 29, 2007 caused to be served by hand delivery the foregoing document and electronically filed the same with the Clerk of Court using CM/ECF which will send notification of such filing(s) to the following:

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I hereby certify that on May 29, 2007, I caused to be sent by Federal Express the foregoing document to the following non-registered participant:

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EXHIBIT A

IN THE UNITED STATES DISTRICT COURT FOR THE
DISTRICT OF DELAWARE

ABBOTT LABORATORIES and
ABBOTT CARDIOVASCULAR
SYSTEMS, INC.,

Plaintiffs,

v.

C. A. No. 06-613-SLR

JOHNSON AND JOHNSON, INC. and
CORDIS CORPORATION,

Defendants.

**[PROPOSED] ORDER GRANTING PLAINTIFFS' MOTION
AND SUPPLEMENTAL MOTION FOR LEAVE
TO FILE A SUPPLEMENTAL COMPLAINT**

At Wilmington this _____ day of _____, 2007, having considered Plaintiffs' Motion For Leave To File A Supplemental Complaint Or In The Alternative To Consolidate Related Actions ("First Motion To Supplement") and Plaintiffs' Supplemental Motion For Leave To File A Supplemental Complaint Or In The Alternative Consolidate Related Actions ("Supplemental Motion to Supplement"),

IT IS HEREBY ORDERED that Plaintiffs' First Motion To Supplement and Supplemental Motion to Supplement are GRANTED. ~~Within 10 days of entry of this Order, Plaintiffs may file a Supplemental and Amended Complaint substantially in the form as Exhibit 1 filed in support of Plaintiffs' Supplemental Motion to Supplement.~~

With the exception of Claim V, the complaint shall be deemed filed as of the filing of the

First Motion to Supplement. Claim V is deemed filed as of the filing of the Supplemental Motion to Supplement.

Chief Judge

EXHIBIT B

IN THE UNITED STATES DISTRICT COURT FOR THE
DISTRICT OF DELAWARE

ABBOTT LABORATORIES and)	
ABBOTT CARDIOVASCULAR)	
SYSTEMS, INC.,)	
)	
Plaintiffs,)	
)	
v.)	C. A. No. 06-613-SLR
)	
JOHNSON AND JOHNSON, INC. and)	
CORDIS CORPORATION,)	
)	
Defendants.)	

**[PROPOSED] ORDER GRANTING PLAINTIFFS' MOTION AND
SUPPLEMENTAL MOTION TO CONSOLIDATE RELATED ACTIONS AND
GRANTING PLAINTIFFS' MOTION FOR LEAVE TO FILE A
SUPPLEMENTAL COMPLAINT**

At Wilmington this _____ day of _____, 2007, having considered (1) Plaintiffs' Motion For Leave To File A Supplemental Complaint Or In The Alternative To Consolidate Related Actions filed in Civil Action No. 06-613-SLR ("Plaintiffs' 06-613 Motion to Consolidate"); (2) Plaintiffs' Supplemental Motion For Leave To File A Supplemental Complaint Or In The Alternative To Consolidate Related Actions filed in Civil Action No. 06-613-SLR ("Plaintiffs' 06-613 Supplemental Motion to Consolidate"); and (3) Plaintiffs' Motion For Leave To File A Supplemental Complaint filed in Civil Action No. 07-259 ("Plaintiffs' 07-259 Motion to Supplement"),

IT IS HEREBY ORDERED that Plaintiffs' 07-259 Motion to Supplement is GRANTED. Within 10 days of entry of this Order, Plaintiffs may file an Amended and Supplemental Complaint substantially in the form as Exhibit 1 filed in support of

Plaintiffs' 07-259 Motion to Supplement. Plaintiffs' Amended and Supplemental Complaint is deemed filed as of the filing of Plaintiffs' 07-259 Motion to Supplement.

IT IS HEREBY ORDERED that Plaintiffs' 06-613 Motion to Consolidate, renewed in Plaintiffs' 06-613 Supplemental Motion to Consolidate, is GRANTED. Civil Action No. 07-259-SLR, filed on May 15, 2007, is hereby consolidated with Civil Action No. 06-613-SLR. Plaintiffs' Complaint for Declaratory Judgment Of Patent Invalidity And Noninfringement for United States Patent No. 7,217,286 filed in Civil Action No. 07-259, is deemed filed as of the filing of Plaintiffs' 06-613 Motion.

Chief Judge

IN THE UNITED STATES DISTRICT COURT FOR THE
DISTRICT OF DELAWARE

ABBOTT LABORATORIES and ABBOTT)
CARDIOVASCULAR SYSTEMS, INC.,)

Plaintiffs,)

v.)

JOHNSON AND JOHNSON, INC. and)
CORDIS CORPORATION,)

Defendants.)

Civil Action No. 06-613-SLR

JURY TRIAL DEMANDED

**SUPPLEMENTAL AND AMENDED COMPLAINT FOR DECLARATORY
JUDGMENT OF PATENT INVALIDITY AND NONINFRINGEMENT**

Plaintiffs Abbott Laboratories and Abbott Cardiovascular Systems, Inc. (collectively “Abbott”) bring this Supplemental and Amended Complaint against Defendants Johnson and Johnson, Inc. and Cordis Corporation (collectively “J&J”). This is an action for a declaratory judgment and injunctive relief that United States Patent No. 6,585,764 entitled “Stent With Therapeutically Active Dosage Of Rapamycin Coated Thereon” (the “Wright ’764 patent”), United States Patent No. 6,808,536 entitled “Stent Containing Rapamycin Or Its Analogs Using A Modified Stent” (the “Wright ’536 patent”), United States Patent No. 6,776,796 entitled “Antiinflammatory Drug and Delivery Device” (the “Falotico ’796 patent”), United States Patent No. 7,217,286 entitled “Local Delivery of Rapamycin for Treatment of Proliferative Sequelae Associated with PTCA Procedures, Including Delivery Using a Modified Stent” (the “Wright ’7286 patent”), and United States Patent No. 7,223,286 entitled “Local Delivery Of Rapamycin For Treatment Of Proliferative Sequelae Associated With PTCA Procedures, Including Delivery Using A Modified Stent” (the “Wright ’3286 patent”) are invalid and not infringed by Abbott.

The Wright '764 patent, the Wright '536 patent, the Falotico '796 patent, and the Wright '7286 patent are attached as Exhibits A – D, respectively. The Issue Notification for the Wright '3286 patent and the Wright '3286 patent are attached as Exhibit E. Abbott alleges as follows:

THE PARTIES

1. Abbott Laboratories is a corporation organized under the laws of the State of Illinois and has a principal place of business at 100 Abbott Park Road, North Chicago, Illinois.

2. Abbott Cardiovascular Systems, Inc. (“ACS”), formerly Advanced Cardiovascular Systems, Inc., is a corporation organized under the laws of the State of California and has a principal place of business at 3200 Lakeside Drive, Santa Clara, California. ACS is a subsidiary of Abbott Laboratories.

3. On information and belief, Johnson and Johnson, Inc. is a corporation organized under the laws of the State of New Jersey and has a principal place of business at One Johnson and Johnson Plaza, New Brunswick, New Jersey.

4. On information and belief, Cordis Corporation (“Cordis”) is a corporation organized under the laws of the State of Florida and has a principal place of business in Miami Lakes, Florida. Cordis is a subsidiary of Johnson and Johnson, Inc.

JURISDICTION AND VENUE

5. This action arises under the Patent Laws of the United States (35 U.S.C. § 1 *et seq.*).

6. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

7. This Court has personal jurisdiction, general and specific, over J&J.

8. On information and belief, J&J has systematic and continuous contacts in this judicial district.

9. On information and belief, J&J regularly avails itself of the benefits of this judicial district, including the jurisdiction of the courts.

10. On information and belief, J&J regularly transacts business within this judicial district.

11. On information and belief, J&J regularly sells products in this judicial district. J&J derives substantial revenues from sales in this district.

12. Venue is proper in this district under 28 U.S.C. §§ 1391(b) and (c).

BACKGROUND

13. J&J, and in particular Cordis, directly competes with Abbott in the field of intravascular stents used to treat coronary artery disease.

14. The coronary stent industry is highly litigious. J&J, and in particular Cordis, has a well-known history of suing competitors in this field for patent infringement.

15. On three occasions within the last ten years, Cordis sued ACS in this district, alleging patent infringement involving angioplasty catheters or stents for treating coronary artery disease. (*Cordis Corporation, et al. v. Advanced Cardiovascular Systems, Inc, et al.*, C.A. No. 97-550-SLR; *Cordis Corporation, et al. v. Advanced Cardiovascular Systems, Inc., et al.*, C.A. No. 97-635-SLR; and *Cordis Corporation, et al. v. Advanced Cardiovascular Systems, Inc., et al.*, C.A. No. 98-065-SLR).

16. On three additional occasions within the last ten years, Cordis initiated patent infringement actions in this judicial district involving angioplasty catheters or stents for treating coronary artery disease. (*Cordis Corp. v. Boston Scientific Corp.*, C.A. No. 98-197-SLR; *Cordis*

Corp. v. Medtronic AVE, Inc., C.A. No. 00-886-SLR; and *Cordis Corp. v. Boston Scientific Corp.*, C.A. No. 03-027-SLR).

17. In early 2006, J&J and Boston Scientific Corporation (“BSC”) each were bidding to acquire assets of Guidant Corporation (“Guidant”), which at the time was the parent corporation of ACS. In conjunction with BSC’s bid, ACS would be acquired by Abbott Laboratories, which was the ultimate result.

18. One of the key assets of ACS was the XIENCE V drug eluting stent system (“XIENCE V”), which elutes a proprietary drug known as everolimus. ACS holds an exclusive patent license to use everolimus for drug eluting stents. In clinical trials, everolimus has proven superior to other drugs.

19. On information and belief, J&J believed in early 2006 that the XIENCE V would be launched within a few months.

J&J’s Public Threats To Sue For Patent Infringement By XIENCE V

20. On information and belief, J&J undertook a public campaign to cast a cloud over the launch of the XIENCE V.

21. On information and belief, as a main thrust of this public campaign, J&J alleged that the XIENCE V would infringe patents allegedly owned by J&J and that J&J would sue Abbott for infringement by the XIENCE V following its launch. On information and belief, J&J’s allegations related to at least the Wright ’764 patent, the Wright ’536 patent, and the Falotico ’796 patent.

22. On information and belief, J&J broadcasted threatening statements to industry analysts regarding alleged infringement by XIENCE V, for publication in furtherance of J&J’s public campaign.

23. For example, the Prudential Equity Group, LLC published a report on January 20, 2006, titled “JNJ: Takes Off The Gloves In Its Fight With Boston Scientific For Guidant,” attached as Exhibit F (“the Prudential report”). In the Prudential report, parties are identified by their stock symbols: ABT for Abbott, GDT for Guidant, JNJ for J&J, and BSX for BSC.

24. On information and belief, the Prudential report relied on information provided in pertinent part by J&J.

25. Among other things, the Prudential report stated:

JNJ claims that 2 of its patents may be infringed if a company tries to launch a drug-eluting stent coated with a rapamycin derivative such as . . . GDT’s everolimus. The potential for JNJ to prevent ABT and BSX from marketing the Xience-V DES, could give the GDT board pause for approving a BSX-GDT merger.

* * *

If BSX acquires GDT, BSX would sell GDT’s vascular intervention (VI) business, including shared rights to GDT’s promising everolimus-coated stent, Xience-V, to ABT. Although JNJ’s patents have never been litigated, JNJ believes it has a strong intellectual property (IP) position with regard to the use of rapamycin derivatives on a stent. JNJ could pursue a preliminary injunction if ABT and BSX try to launch an everolimus-coated . . . stent. . . . According to JNJ, the key patents are the Falotico (6,776,796) and Wright (6,585,764) patents.

26. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Prudential analysts.

27. On January 23, 2006, A.G. Edwards & Sons, Inc. published a report titled “Healthcare Industry Note: The Game May Be Far From Over,” attached as Exhibit G (“the AG Edwards report”).

28. On information and belief, the AG Edwards report relied on information provided in pertinent part by J&J.

29. Among other things, the AG Edwards report stated:

We have had conversations with Johnson & Johnson (JNJ) and Boston Scientific (BSX) and others recently that lead us to believe that the Guidant (GDT) game is far from over.

* * *

We were also reminded by JNJ that it had three patents related to ‘-limus’ compounds that it thought precluded any other company from using such a compound on a stent. We were only given two patent numbers (6776796 [the Falotico ’796 patent] and 6585764 [the Wright ’764 patent])

30. On information and belief, the third patent referenced in J&J’s threatening statements was the Wright ’536 patent.

31. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to AG Edwards analysts.

32. On January 13, 2006, Citigroup published a report titled “An INTERESTing New Offer,” attached as Exhibit H (“the January 13, 2006 Citigroup report”).

33. On information and belief, the January 13, 2006 Citigroup report relied on information provided in pertinent part by J&J.

34. Among other things, the January 13, 2006 Citigroup report stated:

The [Wright and Falotico] patents have never been challenged or enforced because no other company has launched a limus-based drug-eluting stent in the US, but are likely to eventually lead to litigation.

35. Citigroup published an additional report on March 23, 2006 titled “Deconstructing Xience,” attached as Exhibit I (“the March 23, 2006 Citigroup report”). In the March 23, 2006 Citigroup report J&J is identified by its stock symbol JNJ.

36. On information and belief, the March 23, 2006 Citigroup report relied on information provided in pertinent part by J&J.

37. Among other things, the March 23, 2006 Citigroup report stated:
Everolimus will likely face two IP challenges from JNJ as both its Falotico and Wright patents claim the use of a limus analogue on a stent.

38. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Citigroup analysts.

39. On January 30, 2006, Lehman Brothers published a report titled “BSX: The Risks – Part I,” attached as Exhibit J (“the Lehman Brothers report”). In the Lehman Brothers report, parties are identified by their stock symbols: ABT for Abbott; GDT for Guidant; and JNJ for J&J.

40. On information and belief, the Lehman Brothers report relied on information provided in pertinent part by J&J.

41. Among other things, the Lehman Brothers report stated:
There are even hypothetical litigations to contend with as JNJ has strongly suggested that they feel GDT and ABT may violate JNJ/Wyeth DES patents covering the “limus” family of drugs.

42. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Lehman Brothers analysts.

43. On March 14, 2006, Merrill Lynch published a report titled "More legal wrangling for J&J possible," attached as Exhibit K ("the Merrill Lynch report"). In the Merrill Lynch report, J&J is identified by its stock symbol JNJ.

44. On information and belief, the Merrill Lynch report relied on information provided in pertinent part by J&J.

45. Among other things, the Merrill Lynch report stated:

JNJ has two patents (Wright and Falotico) which appear to relate to the elution of characteristics of "olimus" compounds; JNJ's Cypher DES uses sirolimus, a member of the olimus family of drugs; other olimus drugs include Guidant's everolimus and Abbott/Medtronic's zotarolimus (ABT-578). The European launch of Guidant's Xience DES, which the company has targeted for Q2:06, could trigger possible legal activity since we understand U.S. patent law prohibits domestic manufacture of a product for sale outside the U.S. if there's been infringement of intellectual property.

46. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Merrill Lynch analysts.

47. On information and belief, J&J broadcast threatening statements to other news outlets regarding alleged infringement by XIENCE V, for publication in furtherance of J&J's public campaign.

48. On January 23, 2006, the International Herald Tribune published an article headlined "J&J works to discredit rival offer for Guidant," attached as Exhibit L ("the International Herald article").

49. On information and belief, the International Herald article relied on information provided in pertinent part by J&J.

50. Among other things, the International Herald article stated:

"J&J is communicating to the Street that Boston Scientific's \$80-a-share offer for Guidant is fraught with uncertainty," Lawrence Biegelsen, an analyst with Prudential in New York, said in a note to clients sent on Friday.

* * *

Johnson & Johnson's campaign consists of telling analysts and shareholders that Boston Scientific is in over its head and is tempting patent litigation that may undercut Boston Scientific's plans.

"They're trying to tell all of us that there are patents out there that they have that they feel can stop Boston Scientific," said Jan David Wald, an analyst with A.G. Edwards. Wald said he had been called by a Johnson & Johnson employee, whom he declined to name.

Johnson & Johnson told analysts it was considering filing patent infringement lawsuits over stent drug coatings to keep Boston Scientific and its bidding partner, Abbott Laboratories, from profiting from the new Guidant devices, according to Biegelsen of Prudential.

* * *

Boston Scientific and J&J have been fighting in court for years over patent-infringement cases related to stent design. At the moment, the two companies are alone in the U.S. stent market, with Boston Scientific holding a 55 percent share.

* * *

The potential for Johnson & Johnson to prevent Abbott and Boston Scientific from marketing Guidant's next-generation heart stent "could give the Guidant board pause for approving a Boston Scientific-Guidant merger," Biegelsen said. "J&J claims that two of its patents may be infringed if a company tries to launch a drug-eluting stent coated with" . . . Guidant's everolimus, he wrote.

51. On January 20, 2006, the Boston Globe published an article headlined "Suitors take Guidant fight to The Street," attached as Exhibit M ("the Boston Globe article").

52. On information and belief, the Boston Globe article relied on information provided in pertinent part by J&J.

53. Among other things, the Boston Globe article stated:

[J&J] has also raised the prospect that it could use patents and existing ties to Guidant to derail or complicate Boston Scientific's offer, said Matthew Dodds, an analyst for Citigroup who is skeptical about Guidant's value to both companies.

54. Also on January 20, 2006, Crain's Chicago Business published an article headlined "Abbott stock falls on concerns over success of Guidant bid," attached as Exhibit N ("the Crain's article").

55. On information and belief, the Crain's article relied on information provided in pertinent part by J&J.

56. Among other things, the Crain's article stated:

The analyst, Prudential Equity Group, LLC's Larry Biegelsen, reported that Guidant's board could balk at Boston Scientific and Abbott's joint bid because Johnson & Johnson, a competing bidder for Guidant, claims its patents would be violated if Abbott markets its own drug-eluting stents or those made by Guidant.

57. On January 21, 2006, Reuters published an article headlined "Abbott, Boston shares off on J&J patent threat," attached as Exhibit O ("the Reuters article").

58. On information and belief, the Reuters article relied on information provided in pertinent part by J&J.

59. Among other things, the Reuters article stated:

One analyst, who asked not to be named, said J&J management was making rounds on Wall Street trying to fan fears about the Boston Scientific bid.

The analyst said J&J was arguing that Boston Scientific's bid was breaking its bank, that its assumptions on Guidant's cardiac rhythm management were too aggressive and that there was intellectual property infringement that would limit potential of important products.

60. On January 24, 2006, Medical Device Daily published an article headlined "J&J offer rumors persist as Guidant has more ICD issues," attached as Exhibit P ("the Medical Device Daily article").

61. On information and belief, the Medical Device Daily article relied on information provided in pertinent part by J&J.

62. Among other things, the Medical Device Daily article stated:

Fueling this speculation were rumors, some of which apparently were planted by J&J personnel as part of an organized campaign to undermine the Boston

Scientific offer in the minds of analysts, that two of its patents may be infringed if an unnamed company tries to launch a drug-eluting stent coated with a derivative of rapamycin.

63. On January 26, 2006, The Wall Street Journal published an article headlined "Boston Scientific Faces Pivotal Test After Victory in Fight for Guidant," attached as Exhibit Q ("the Wall Street Journal article").

64. On information and belief, the Wall Street Journal article relied on information provided in pertinent part by J&J.

65. Among other things, the Wall Street Journal article stated that:
Another potential wrinkle arises in the intellectual-property rights surrounding stents -- an area that's been the subject of extensive litigation in the industry. Citigroup analyst Matthew Dodds says J&J holds patents on methods of using "limus"-type drugs on stents -- including the everolimus on Guidant's stent, as well as a drug on an Abbott stent.

66. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to analysts and others.

67. On information and belief, J&J made additional threatening statements to industry analysts, asserting that J&J could prevent Abbott from making or selling the XIENCE V by suing for infringement of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent. On information and belief, J&J anticipated and intended that Abbott and others would become aware of these threatening statements.

68. Abbott and others did become aware of J&J's threatening statements.

69. For example, on January 20, 2006, Avram Goldstein of Bloomberg contacted Abbott regarding the Wright and Falotico patents in relation to XIENCE V.

70. On January 13, 2006, Bruce Nudell of Sanford C. Bernstein contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

71. Also on January 13, 2006, The Shaw Group contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

72. On January 20, 2006, Avram Goldstein of Bloomberg contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

73. Again on January 20, 2006, Barnaby Feder of the New York Times contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

74. On January 31, 2006, Steve Silva of Joele Frank contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

75. On March 23, 2006, Jennifer B. Pearlman of Burgundy Asset Management contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

76. On information and belief, in furtherance of its campaign to cast a cloud over the launch of XIENCE V, J&J made threatening statements to Guidant.

77. On January 12, 2006, J&J contacted Guidant and informed Guidant that if Boston Scientific acquired Guidant, Abbott and Boston Scientific would have problems with the Wright and Falotico patent families.

78. On January 13, 2006, J&J again contacted Guidant. J&J sent Guidant a document asserting that J&J's intellectual property portfolio included patents directed to everolimus when used on a stent, Abbott would not receive access to these patents in the event that Boston

Scientific were to acquire Guidant, and any drug eluting stent using everolimus, including XIENCE V, may infringe these patents.

79. On information and belief, J&J intended to create a substantial controversy between J&J and Abbott regarding XIENCE V's alleged infringement of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

80. On information and belief, J&J intended to create the apprehension in Abbott and others that J&J would sue Abbott, following the launch of the XIENCE V, asserting that the XIENCE V allegedly infringes the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

81. In March 2006, Guidant publicly announced that the XIENCE V launch would be delayed due to an issue related to manufacturing.

82. As of the date of the original Complaint, the XIENCE V launch was imminent. On information and belief, J&J was aware that the XIENCE V launch was imminent and was preparing to sue Abbott for infringement by the XIENCE V of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent. The XIENCE V subsequently launched in Europe.

83. On information and belief, J&J has never withdrawn or retracted any of its threatening statements that, following the launch of the XIENCE V, J&J would sue Abbott for infringement of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

84. On information and belief, by these statements J&J intended to create a substantial controversy between J&J and Abbott regarding alleged infringement of patents in the Wright and/or Falotico families by XIENCE V.

85. On information and belief, by these statements J&J intended to create the apprehension in Abbott and others that J&J would sue Abbott, following the launch of XIENCE V, asserting that XIENCE V allegedly infringes patents in the Wright and/or Falotico families.

J&J's Assertions In The Patent Office Of Infringement By XIENCE V

86. On August 7, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the First Wright Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 10/951,385 ("Wright '385 application"). The Wright '385 application is related to the Wright '764 patent, the Wright '536 patent, and the Wright '7286 patent. On information and belief, on May 29, 2007, the Wright '385 application issued as the Wright '3286 patent. A copy of the First Wright Petition is attached as Exhibit R.

87. In the First Wright Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Wright '385 application as a patent. Among other things, counsel for J&J asserted:

Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch XIENCETM V in Europe in the third quarter of 2006 (Exhibit 4).

* * *

I have made a rigid comparison of the XIENCETM V product, as described in Guidant press releases, with the claims of the instant application. In my opinion, the XIENCETM V product is unquestionably within the scope of at least claims 103 and 130 on file in this application.

* * *

It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of at least claims 103 and 130 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

88. The subject matter of at least claim 103 of the Wright '385 application overlaps with subject matter claimed in the Wright '764 patent and the Wright '536 patent. On information and belief, claim 103 of the Wright '385 application issued on May 29, 2007 as claim 40 of the Wright '3286 patent.

89. On information and belief, the subject matter claimed in the Wright '3286 patent is not patentably distinct from subject matter claimed in at least the Wright '7286 patent, the Wright '764 patent, the Wright '536 patent, and/or United States Application Serial No. 11/466,983 ("the Wright '983 application").

90. On August 24, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the Second Wright Petition") with the United States Patent and Trademark Office in the matter of the Wright '983 application. The Wright '983 application is related to the Wright '764 patent, the Wright '536 patent, and the Wright '3286 patent. A copy of the Second Wright Petition is attached as Exhibit S.

91. In the Second Wright Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Wright '983 application as a patent. In the Second Wright Petition, J&J's counsel made assertions substantially identical to the assertions made in connection with the First Wright Petition. (*See supra* ¶ 87).

92. The subject matter of at least claim 1 of the Wright '983 application overlaps with subject matter claimed in the Wright '764 patent.

93. On information and belief, the subject matter claimed in the Wright '983 application is not patentably distinct from subject matter claimed in at least the Wright '7286 patent, the Wright '3286 patent, the Wright '764 patent, and/or the Wright '536 patent.

94. On August 24, 2006, J&J filed another "Petition to Make Special Because of Actual Infringement" ("the Third Wright Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 11/467,035 ("the Wright '035 application"). The Wright '035 application is related to the Wright '764 patent, the Wright '536 patent, and the Wright '3286 patent. On May 15, 2007, the Wright '035 application issued as the Wright '7286 patent. A copy of the Third Wright Petition is attached as Exhibit T.

95. In the Third Wright Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Wright '035 application as a patent. In the Third Wright Petition, J&J's counsel made assertions substantially identical to the assertions made in connection with the First Wright Petition. (*See supra* ¶ 87).

96. The subject matter of at least claim 1 of the Wright '7286 patent overlaps with subject matter claimed in the Wright '764 patent.

97. The subject matter claimed in the Wright '7286 patent is not patentably distinct from subject matter claimed in at least the Wright '3286 patent, the Wright '983 application, the Wright '764 patent, and/or the Wright '536 patent.

98. On information and belief, J&J is preparing to assert, and has asserted, one or more patents in the Wright family, including at least the Wright '764 patent, the Wright '536 patent, the Wright '7286 patent, and the Wright '3286 patent against the XIENCE V.

99. On August 7, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the First Falotico Petition") with the United States Patent and Trademark Office

in the matter of United States Application Serial No. 10/829,074 (“the Falotico ’074 application”). The Falotico ’074 application is related to the Falotico ’796 patent. A copy of the First Falotico Petition is attached as Exhibit U.

100. In the First Falotico Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Falotico ’074 application as a patent. Among other things, counsel for J&J asserted:

Guidant’s vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

* * *

I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases and other publicly available documents, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of claims 15 to 30 on file in this application.

* * *

It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of claims 15 to 30 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

101. The subject matter of at least claim 15 of the Falotico ’074 application overlaps with subject matter claimed in the Falotico ’796 patent.

102. On August 7, 2006, J&J filed a “Petition to Make Special Because of Actual Infringement” (“the Second Falotico Petition”) with the United States Patent and Trademark

Office in the matter of United States Application Serial No. 10/852,517 (“the Falotico ’517 application”). The Falotico ’517 application is related to the Falotico ’796 patent. A copy of the Second Falotico Petition is attached as Exhibit V.

103. In the Second Falotico Petition, J&J asserted that it could sue Abbott for infringement by XIENCE V immediately upon issuance of the Falotico ’517 application as a patent. In the Second Falotico Petition, J&J’s counsel made assertions substantially identical to the assertions made in connection with the First Falotico Petition. (*See supra* ¶ 100).

104. The subject matter of at least claim 5 of the Falotico ’517 application overlaps with subject matter claimed in the Falotico ’796 patent.

105. On August 24, 2006, J&J filed a “Petition to Make Special Because of Actual Infringement” (“the Third Falotico Petition”) with the United States Patent and Trademark Office in the matter of United States Application Serial No. 11/467,099 (“the Falotico ’099 application”). The Falotico ’099 application is related to the Falotico ’796 patent. A copy of the Third Falotico Petition is attached as Exhibit W.

106. In the Third Falotico Petition, J&J asserted that it could sue Abbott for infringement by XIENCE V immediately upon issuance of the Falotico ’099 application as a patent. In the Third Falotico Petition, J&J’s counsel made assertions substantially identical to the assertions made in connection with the First Falotico Petition. (*See supra* ¶ 100).

107. The subject matter of at least claim 1 of the Falotico ’099 application overlaps with subject matter claimed in the Falotico ’796 patent.

108. On information and belief, J&J is preparing to assert one or more patents in the Falotico family, including at least the Falotico ’796 patent, against the XIENCE V.

J&J Has Recently Sued Abbott In An Attempt To Interfere With The XIENCE V Launch

109. On September 25, 2006, J&J filed a complaint in the District Court for the Southern District of New York. Among other things, J&J alleges that Abbott Laboratories tortiously interfered with J&J's intended acquisition of Guidant. The complaint seeks no less than \$5.5 billion in damages. A copy of the complaint is attached as Exhibit X.

110. Although the events cited in the complaint occurred over eight months ago, J&J timed the lawsuit, on information and belief, in anticipation of the then imminent launch of XIENCE V. Both the timing of the lawsuit and the amount of the damages claimed manifest J&J's intent to cast a cloud over Abbott and interfere with the then imminent launch of the XIENCE V.

The XIENCE V Launch

111. As of the date of the original Complaint, Abbott had manufactured, at its facilities in the United States, thousands of XIENCE V products to support its launch.

112. Abbott has continued to manufacture XIENCE V at its facilities in the United States following the launch.

113. J&J created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Wright '764 patent, the Wright '536 patent, the Falotico '796 patent, the Wright '7286 patent, and the Wright '3286 patent by XIENCE V.

114. Abbott has a reasonable apprehension that J&J intends to sue Abbott for infringement of the Wright '764 patent, the Wright '536 patent, the Falotico '796 patent, the Wright '7286 patent, and the Wright '3286 patent by XIENCE V.

CLAIM I

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 6,585,764

115. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-114.

116. J&J's actions have created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Wright '764 patent by XIENCE V.

117. J&J has asserted rights under the Wright '764 patent against the XIENCE V.

118. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '764 patent by XIENCE V.

119. On information and belief, the claims of the Wright '764 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

120. The XIENCE V does not infringe any valid claim of the Wright '764 patent.

121. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '764 patent.

CLAIM II

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 6,808,536

122. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-121.

123. J&J's actions have created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Wright '536 patent by XIENCE V.

124. J&J has asserted rights under the Wright '536 patent against the XIENCE V.

125. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '536 patent by XIENCE V.

126. On information and belief, the claims of the Wright '536 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

127. The XIENCE V does not infringe any valid claim of the Wright '536 patent.

128. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '536 patent.

CLAIM III

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 6,776,796

129. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-128.

130. J&J's actions have created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Falotico '796 patent by XIENCE V.

131. J&J has asserted rights under the Falotico '796 patent against the XIENCE V.

132. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Falotico '796 patent by XIENCE V.

133. On information and belief, the claims of the Falotico '796 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

134. The XIENCE V does not infringe any valid claim of the Falotico '796 patent.

135. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Falotico '796 patent.

CLAIM IV

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 7,217,286

136. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-135.

137. The Wright '7286 patent issued on May 15, 2007.

138. J&J's actions have created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Wright '7286 patent by XIENCE V.

139. J&J has asserted rights under the Wright '7286 patent against the XIENCE V.

140. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '7286 patent by XIENCE V.

141. On information and belief, the claims of the Wright '7286 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

142. The XIENCE V does not infringe any valid claim of the Wright '7286 patent.

143. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '7286 patent.

CLAIM V

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 7,223,286

144. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-143.

145. On information and belief, the Wright '3286 patent issued on May 29, 2007.

146. J&J's actions have created a substantial controversy between J&J and Abbott regarding alleged infringement of the Wright '3286 patent by XIENCE V.

147. J&J has asserted rights under the Wright '3286 patent against the XIENCE V.

148. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '3286 patent by XIENCE V.

149. On information and belief, the claims of the Wright '3286 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103 and 112.

150. The XIENCE V does not infringe any valid claim of the Wright '3286 patent.

151. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '3286 patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request entry of judgment in their favor that:

- (a) each and every claim of U.S. Patent No. 6,585,764 is invalid;
- (b) each and every claim of U.S. Patent No. 6,808,536 is invalid;
- (c) each and every claim of U.S. Patent No. 6,776,796 is invalid;
- (d) each and every claim of U.S. Patent No. 7,217,286 is invalid;
- (e) each and every claim of U.S. Patent No. 7,223,286 is invalid;
- (f) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 6,585,764;
- (g) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 6,808,536;
- (h) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 6,776,796;

(i) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 7,217,286;

(j) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 7,223,286;

(k) Defendants and their officers, agents, employees, representatives, counsel and all persons in active concert or participation with any of them, directly or indirectly, be enjoined from threatening or charging infringement of, or instituting any action for infringement of any of U.S. Patent Nos. 6,585,764, 6,808,536, 6,776,796, 7,217,286, and 7,223,286 against Plaintiffs, their suppliers, customers, distributors or users of their products;

(l) Defendants pay to Plaintiffs the costs and reasonable attorneys fees incurred by Plaintiffs in this action; and

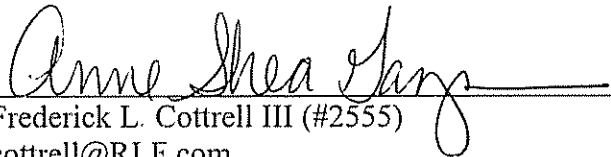
(m) Plaintiffs be granted such other and further relief as this Court deems just and proper.

JURY TRIAL DEMANDED

Plaintiffs demand a trial by jury on all issues so triable.

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Date: May 29, 2007

Exhibit A



US006585764B2

(12) **United States Patent**
Wright et al.

(10) **Patent No.:** **US 6,585,764 B2**
(45) **Date of Patent:** **Jul. 1, 2003**

(54) **STENT WITH THERAPEUTICALLY ACTIVE
DOSAGE OF RAPAMYCIN COATED
THEREON**

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(List continued on next page)

FOREIGN PATENT DOCUMENTS

(73) **Assignee:** **Cordis Corporation, Miami Lakes, FL
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(*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days

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(21) **Appl. No.:** **09/874,117**

(22) **Filed:** **Jun. 4, 2001**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 09/061,568, filed on Apr.
16, 1998, now Pat. No. 6,273,913.

(60) Provisional application No. 60/044,692, filed on Apr. 18,
1997.

(51) **Int. Cl.⁷** **A61F 2/06**

(52) **U.S. Cl.** **623/1.42**

(58) **Field of Search** **623/1.15, 1 39,
623/1.42, 1 4; 427/2 1-2 31**

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Primary Examiner—David H. Willse

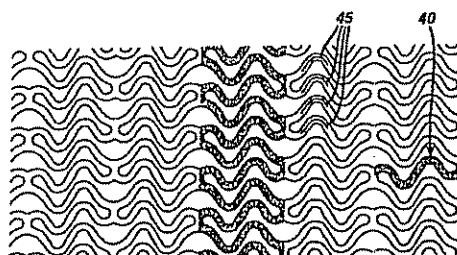
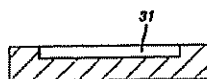
Assistant Examiner—Suzette J. Jackson

(74) *Attorney, Agent, or Firm*—Paul A. Coletti

(57) **ABSTRACT**

Delivery of rapamycin locally, particularly from intravascu-
lar stent, directly from micropores in the stent body or mixed
or bound to a polymer coating applied on stent, to inhibit
neointimal tissue proliferation and thereby prevent resteno-
sis. This invention also facilitates the performance of the
stent in inhibiting restenosis.

20 Claims, 2 Drawing Sheets



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Page 2

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FIG. 1

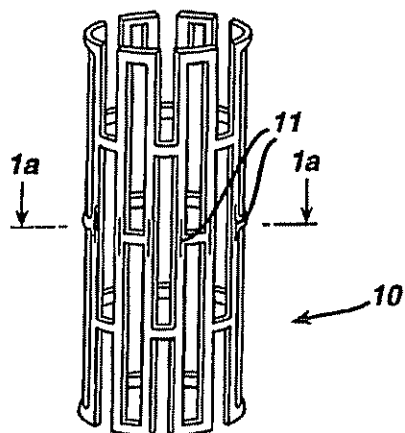


FIG. 1a

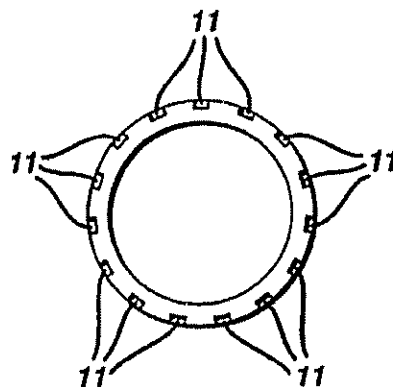


FIG. 2a

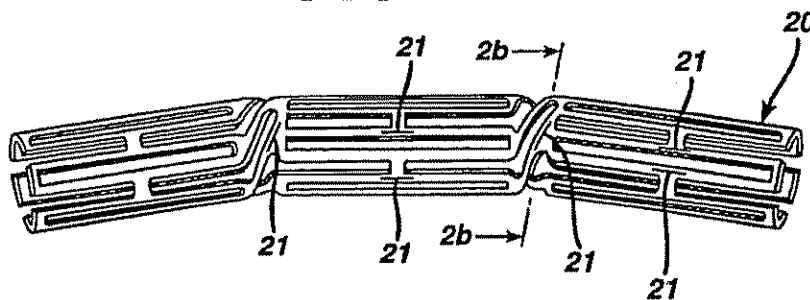
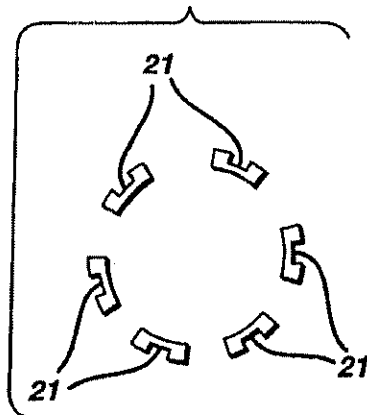


FIG. 2b



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FIG. 3a

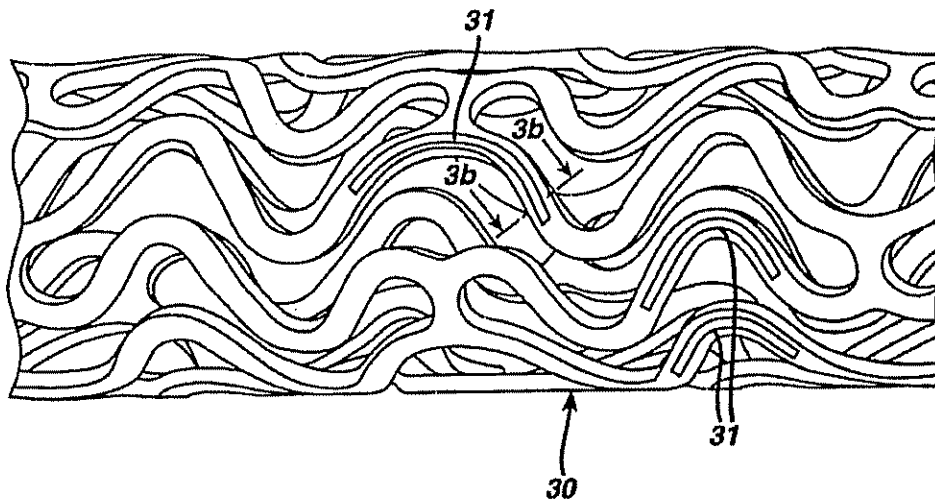


FIG. 3b

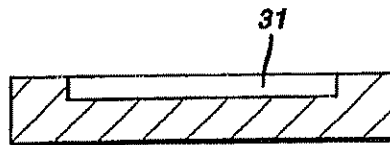
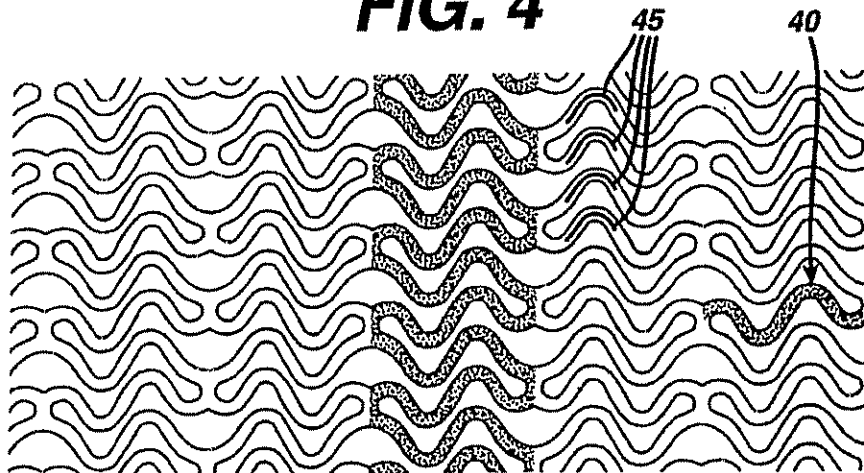


FIG. 4



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STENT WITH THERAPEUTICALLY ACTIVE DOSAGE OF RAPAMYCIN COATED THEREON

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of U.S. application Ser. No. 09/061,568, filed Apr. 16, 1998, now issued as U.S. Pat. No. 6,273,913, which claims the benefit of U.S. Provisional Application No. 60/044,692, filed Apr. 18, 1997.

FIELD OF THE INVENTION

Delivery of rapamycin locally, particularly from an intra-vascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

BACKGROUND OF THE INVENTION

Re-narrowing (restenosis) of an atherosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10–50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft. While the exact hormonal and cellular processes promoting restenosis are still being determined, our present understanding is that the process of PTCA, besides opening the atherosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC). In response to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3–6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow.

Several recent experimental approaches to preventing SMC proliferation have shown promise although the mechanisms for most agents employed are still unclear. Heparin is the best known and characterized agent causing inhibition of SMC proliferation both in vitro and in animal models of balloon angioplasty-mediated injury. The mechanism of SMC inhibition with heparin is still not known but may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes c-fos and c-myc, 2) reduced cellular production of tissue plasminogen activator; are 3) binding and dequstration of growth regulatory factors such as fibrovalent growth factor (FGF).

Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers, angiotensin converting enzyme inhibitors (captopril, cilazapril), cyclosporin A, trapidil (an antianginal, antiplatelet agent), terbinafine (antifungal), colchicine and taxol (antitubulin antiproliferatives), and c-myc and c-myb antisense oligonucleotides.

Additionally, a goat antibody to the SMC mitogen platelet derived growth factor (PDGF) has been shown to be effective in reducing myointimal thickening in a rat model of balloon angioplasty injury, thereby implicating PDGF

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directly in the etiology of restenosis. Thus, while no therapy has as yet proven successful clinically in preventing restenosis after angioplasty, the in vivo experimental success of several agents known to inhibit SMC growth suggests that these agents as a class have the capacity to prevent clinical restenosis and deserve careful evaluation in humans.

Coronary heart disease is the major cause of death in men over the age of 40 and in women over the age of fifty in the western world. Most coronary artery-related deaths are due to atherosclerosis. Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500,000–600,000 deaths in the United States annually. To arrest the disease process and prevent the more advanced disease states in which the cardiac muscle itself is compromised, direct intervention has been employed via percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG).

PTCA is a procedure in which a small balloon-tipped catheter is passed down a narrowed coronary artery and then expanded to re-open the artery. It is currently performed in approximately 250,000–300,000 patients each year. The major advantage of this therapy is that patients in which the procedure is successful need not undergo the more invasive surgical procedure of coronary artery bypass graft. A major difficulty with PTCA is the problem of post-angioplasty closure of the vessel, both immediately after PTCA (acute reocclusion) and in the long term (restenosis).

The mechanism of acute reocclusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus. Recently, intravascular stents have been examined as a means of preventing acute reclosure after PTCA.

Restenosis (chronic reclosure) after angioplasty is a more gradual process than acute reocclusion: 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty. While the exact mechanism for restenosis is still under active investigation, the general aspects of the restenosis process have been identified.

In the normal arterial wall, smooth muscle cells (SMC) proliferate at a low rate (<0.1%/day; ref). SMC in vessel wall exists in a 'contractile' phenotype characterized by 80–90% of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, golgi bodies, and free ribosomes are few and located in the perinuclear region. Extracellular matrix surrounds SMC and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining SMC in the contractile phenotypic state.

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the arterial wall become injured. Cell derived growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), etc. released from platelets (i.e., PDGF) adhering to the damaged arterial luminal surface, invading macrophages and/or leukocytes, or directly from SMC (i.e., bFGF) provoke a proliferation and migratory response in medial SMC. These cells undergo a phenotypic change from the contractile phenotype to a 'synthetic' phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum, golgi and free ribosomes. Proliferation/migration usually begins within 1–2 days post-

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injury and peaks at 2 days in the media, rapidly declining thereafter (Campbell et al., In: *Vascular Smooth Muscle Cells in Culture*, Campbell, J. H. and Campbell, G. R., Eds, CRC Press, Boca Ration, 1987, pp. 39-55); Clowes, A. W. and Schwartz, S. M., *Circ. Res.* 56:139-145, 1985).

Finally, daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate. Proliferation and migration continues until the damaged luminal endothelial layer regenerates at which time proliferation ceases within the intima, usually within 7-14 days postinjury. The remaining increase in intimal thickening which occurs over the next 3-6 months is due to an increase in extracellular matrix rather than cell number. Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response. (Liu et al., *Circulation*, 79:1374-1387, 1989).

Patients with symptomatic reocclusion require either repeat PTCA or CABG. Because 30-50% of patients undergoing PTCA will experience restenosis, restenosis has clearly limited the success of PTCA as a therapeutic approach to coronary artery disease. Because SMC proliferation and migration are intimately involved with the pathophysiological response to arterial injury, prevention of SMC proliferation and migration represents a target for pharmacological intervention in the prevention of restenosis.

SUMMARY OF THE INVENTION

Novel Features and Applications to Stent Technology

Currently, attempts to improve the clinical performance of stents have involved some variation of either applying a coating to the metal, attaching a covering or membrane, or embedding material on the surface via ion bombardment. A stent designed to include reservoirs is a new approach which offers several important advantages over existing technologies.

Local Drug Delivery from a Stent to Inhibit Restenosis

In this application, it is desired to deliver a therapeutic agent to the site of arterial injury. The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent. The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks, and be as thin as possible so as to minimize the increase in profile. In addition, the coating material should not contribute to any adverse response by the body (i.e., should be non-thrombogenic, non-inflammatory, etc.). To date, the ideal coating material has not been developed for this application.

An alternative would be to design the stent to contain reservoirs which could be loaded with the drug. A coating or membrane of biocompatible material could be applied over the reservoirs which would control the diffusion of the drug from the reservoirs to the artery wall.

One advantage of this system is that the properties of the coating can be optimized for achieving superior biocompatibility and adhesion properties, without the addition requirement of being able to load and release the drug. The size, shape, position, and number of reservoirs can be used to control the amount of drug, and therefore the dose delivered.

DESCRIPTION OF THE DRAWINGS

The invention will be better understood in connection with the following figures in which

FIGS. 1 and 1a are top views and section views of a stent containing reservoirs as described in the present invention;

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FIGS. 2a and 2b are similar views of an alternate embodiment of the stent with open ends;

FIGS. 3a and 3b are further alternate figures of a device containing a grooved reservoir; and

FIG. 4 is a layout view of a device containing a reservoir as in FIG. 3.

DETAILED DESCRIPTION OF THE INVENTION

Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents. Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty. The calcium antagonists have also been unsuccessful in preventing restenosis, although they are still under study. Other agents currently under study include thromboxane inhibitors, prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al., 42 *Ann. Rev. Med.*, 127-132 (1991); Popma et al., 84 *Circulation*, 1426-1436 (1991)).

Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements, thromboxane receptor antagonists, cholesterol lowering agents, and serotonin antagonists has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Franklin, S. M. and Faxon, D. P., 4 *Coronary Artery Disease*, 232-242 (1993); Serruys, P. W. et al., 88 *Circulation*, (part 1) 1588-1601, (1993)).

Conversely, stents have proven useful in preventing reducing the proliferation of restenosis. Stents, such as the stent 40, seen in layout in FIG. 4, balloon-expandable slotted metal tubes (usually but not limited to stainless steel), which when expanded within the lumen of an angioplastied coronary artery, provide structural support to the arterial wall. This support is helpful in maintaining an open path for blood flow. In two randomized clinical trials, stents were shown to increase angiographic success after PTCA, increase the stenosed blood vessel lumen and to reduce the lesion recurrence at 6 months (Serruys et al., 331 *New Eng Jour. Med.*, 495, (1994); Fischman et al., 331 *New Eng Jour. Med.*, 496-501 (1994). Additionally, in a preliminary trial, heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Additionally, heparin coating appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 93 *Circulation*, 412-422 (1996). Thus, 1) sustained mechanical expansion of a stenosed coronary artery has been shown to provide some measure of restenosis prevention, and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs to local, injured tissue off the surface of the stent.

Numerous agents are being actively studied as antiproliferative agents for use in restenosis and have shown some

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activity in experimental animal models. These include: heparin and heparin fragments (Clowes and Karnovsky, 265 *Nature*, 25-626, (1977); Guyton, J. R. et al. 46 *Circ. Res.*, 625-634, (1980); Clowes, A. W. and Clowes, M. M., 52 *Lab. Invest.*, 611-616, (1985) A. W. and Clowes, M. M., 58 *Circ. Res.*, 839-845 (1986); Majesky et al., 61 *Circ. Res.*, 296-300, (1987); Snow et al., 137 *Am. J. Pathol.*, 313-330 (1990); Okada, T. et al., 25 *Neurosurgery*, 92-898, (1989) colchicine (Currier, J. W. et al., 80 *Circulation*, 11-66, (1989), taxol (ref), angiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., 245 *Science*, 186-188 (1989), angiopeptin (Lundergan, C. F. et al., 17 *Am. J. Cardiol. (Suppl. B)*; 132B-136B (1991), Cyclosporin A (Jonasson, L. et al., 85 *Proc. Natl. Acad. Sci.*, 2303 (1988), goat-anti-rabbit PDGF antibody (Forns, G. A. A., et al., 253 *Science*, 1129-1132 (1991), terbinafine (Nemecek, G. M. et al., 248 *J. Pharmacol. Exp. Ther.*, 1167-11747 (1989), trapidil (Liu, M. W. et al., 81 *Circulation*, 1089-1093 (1990), interferon-gamma (Hansson, G. K. and Holm, 84 *J. Circulation*, 1266-1272 (1991), steroids (Colburn, M. D. et al., 15 *J. Vasc. Surg.*, 510-518 (1992), see also Berk, B. C. et al., 17 *J. Am. Coll. Cardiol.*, 111B-117B (1991), ionizing radiation (ref), fusion toxins (ref) antisense oligonucleotides (ref), gene vectors (ref), and rapamycin (see below).

Of particular interest is rapamycin. Rapamycin is a macrolide antibiotic which blocks IL-2-mediated T-cell proliferation and possesses antiinflammatory activity. While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G₁ to S phase progression of T-cells through the cell cycle by inhibiting specific cell cyclins and cyclin-dependent protein kinases (Sickierka, *Immunol. Res.* 13: 110-116, 1994). The antiproliferative action of rapamycin is not limited to T-cells; Marx et al. (*Circ. Res.* 76:412-417, 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC in vitro while Poon et al. have shown the rat, porcine, and human SMC migrating can also be inhibited by rapamycin (*J. Clin. Invest.* 98: 2277-2283, 1996). Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response. In fact, the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al., *Transplantation* 55:1409-1418, 1993; Gallo et al., in press, (1997)). These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis.

Although the ideal agent for restenosis has not yet been identified, some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury, including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications. Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of SMC combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

Experiments

Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression.

Delivery Methods:

These can vary:

Local delivery of such agents (rapamycin) from the struts of a stent, from a stent graft, grafts, stent cover or sheath.

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Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft.

or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein.

or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e.g. vapour deposition methods such as rf-plasma polymerization) and combinations thereof.

Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake

Extravascular delivery by the pericardial route

Extravascular delivery by the adventitial application of sustained release formulations.

Uses: for inhibition of cell proliferation to prevent neointimal proliferation and restenosis.

prevention of tumor expansion from stents

prevent ingrowth of tissue into catheters and shunts inducing their failure.

1. Experimental Stent Delivery Method—Delivery from Polymer Matrix

Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0.001 weight % to 30 weight % of drug. Polymers are biocompatible (i.e., not elicit any negative tissue reaction or promote mural thrombus formation) and degradable, such as lactone-based polyesters or copolyesters, e.g., polylactide, polycaprolactone, glycolide, polyorthoesters, polyanhydrides; polyaminoacids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, e.g., PEO-PLLA, or blends thereof. Nonabsorbable biocompatible polymers are also suitable candidates. Polymers such as polydimethylsiloxane; poly(ethylene-vinylacetate); acrylate based polymers or copolymers, e.g., poly(hydroxyethyl methacrylate), polyvinyl pyrrolidone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters.

Polymer/drug mixture is applied to the surfaces of the stent by either dip-coating, or spray coating, or brush coating or dip/spin coating or combinations thereof, and the solvent allowed to evaporate to leave a film with entrapped rapamycin.

2. Experimental Stent Delivery Method—Delivery from Microporous Depots in Stent Through a Polymer Membrane Coating:

Stent, whose body has been modified to contain micropores or channels is dipped into a solution of Rapamycin, range 0.001 wt % to saturated, in organic solvent such as acetone or methylene chloride, for sufficient time to allow solution to permeate into the pores. (The dipping solution can also be compressed to improve the loading efficiency.) After solvent has been allowed to evaporate, the stent is dipped briefly in fresh solvent to remove excess surface bound drug. A solution of polymer, chosen from any identified in the first experimental method, is applied to the stent as detailed above. This outerlayer of polymer will act as diffusion-controller for release of drug.

3. Experimental Stent Delivery Method—Delivery Via Lysis of a Covalent Drug Tether

Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization. Covalent bonds such as ester, amides or anhydrides may be suitable for this.

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4. Experimental Method—Pericardial Delivery

A: Polymeric Sheet Rapamycin is combined at concentration range previously highlighted, with a degradable polymer such as poly(caprolactone-glycolide) or non-degradable polymer, e.g., polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10μ to 1000μ . The resulting sheet can be wrapped perivascularly on the target vessel. Preference would be for the absorbable polymer.

B: Conformal Coating: Rapamycin is combined with a polymer that has a melting temperature just above 37°C , range 40° – 45°C . Mixture is applied in a molten state to the external side of the target vessel. Upon cooling to body temperature the mixture solidifies conformally to the vessel wall. Both non-degradable and absorbable biocompatible polymers are suitable.

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin. As seen in FIGS. 1a, 2a and 3a, any stent strut 10, 20, 30 can be modified to have a certain reservoir or channel 11, 21, 31. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. FIG. 4 shows a stent 40 with a reservoir 45 created at the apex of a flexible strut. Of course, this reservoir 45 is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents.

In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must be kept at a size of about 0.0005" to about 0.003". Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

These and other concepts will be disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be perceived to fall within the scope of the invention which is to be realized from the attached claims and their equivalents.

What is claimed is:

1. A stent having a coating containing rapamycin, said coating formed from a polymer mixed carrier containing the rapamycin; and said coating applied to said stent.

2. The stent of claim 1 wherein the stent is dip-coated.

3. The stent of claim 1 wherein the stent is sprayed with said coating.

4. A stent having a coating containing rapamycin or its analogs, wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0.0001% to 30%.

5. The stent of claim 4 wherein a polymer is mixed to the rapamycin or its analogs.

6. The stent of claim 4 wherein a polymer is bound to the rapamycin or its analogs.

7. The stent of claim 4 wherein the rapamycin or its analogs is entrapped on the surface of the stent by a polymer.

8. A stent having a coating containing rapamycin, said coating formed from a polymer mixed carrier containing the rapamycin or its analogs; and said coating applied to said stent; wherein the polymer is biocompatible and degradable; and

wherein the polymer is chosen from: lactone-based polyesters, lactone-based copolyesters; polyanhy-

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drides; polyaminoacids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, and blends of such polymers.

9. A stent having a coating containing rapamycin, said coating formed from a polymer mixed carrier containing the rapamycin or its analogs; and said coating applied to said stent; and

wherein the polymer is chosen from: lactone-based polyesters, lactone-based copolyesters; polyanhydrides; polyaminoacids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, and blends of such polymers.

10. A stent having a coating containing rapamycin, said coating formed from a polymer mixed carrier containing the rapamycin or its analogs; and said coating applied to said stent; wherein the polymer is nonabsorbable; and

wherein the polymer is chosen from: polydimethylsiloxane; poly(ethylene)vinylacetate; poly(hydroxy)ethylmethacrylate, polyvinyl pyrrolidone; polytetrafluoroethylene; and cellulose esters.

11. A stent having a coating containing rapamycin or its analogs, said coating formed from a polymer mixed carrier containing the rapamycin or its analogs; and said coating applied to said stent; and

wherein the polymer is chosen from: polydimethylsiloxane; poly(ethylene)vinylacetate; poly(hydroxy)ethylmethacrylate, polyvinyl pyrrolidone; polytetrafluoroethylene; and cellulose esters.

12. A stent having a coating containing rapamycin or its analogs, said coating formed from a polymer mixed carrier containing the rapamycin or its analogs; and said coating applied to said stent; and further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said applied to said strut, and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top, and said channel smaller in all dimensions than said strut, said channel containing a reservoir of said rapamycin coating applied therein.

13. A stent having a coating containing rapamycin or its analogs, wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0.0001% to 30%, wherein the coating is a polymer.

14. The stent of claim 13 wherein said polymer is mixed to the rapamycin or its analogs.

15. The stent of claim 4 wherein said polymer is bound to the rapamycin or its analogs.

16. The stent of claim 13 wherein the rapamycin or its analogs is entrapped on the surface of the stent by said polymer.

17. A stent containing a polymer and rapamycin or its analogs wherein said rapamycin or its analogs are contained in a therapeutically beneficial amount to combat restenosis.

18. The stent of claim 17 wherein said polymer is mixed to the rapamycin or its analogs.

19. The stent of claim 17 wherein said polymer is bound to the rapamycin or its analogs.

20. The stent of claim 17 wherein the rapamycin or its analogs is entrapped on the surface of the stent by said polymer.

* * * * *

Exhibit B



US006808536B2

(12) **United States Patent**
Wright et al.

(10) **Patent No.:** US 6,808,536 B2
(45) **Date of Patent:** *Oct. 26, 2004

(54) **STENT CONTAINING RAPAMYCIN OR ITS ANALOGS USING A MODIFIED STENT**

(76) **Inventors:** Carol Wright, 48 Marcy St., Somerset, NJ (US) 08873; Gerard H. Llanos, 1514 Mean Cir., Stewartsville, NJ (US) 08886; Ronald Rakos, 35 Regal Dr., Monmouth Jct, NJ (US); Kristen Kling, 51 Garden St., Apt. 611, Hoboken, NJ (US) 07030

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days

This patent is subject to a terminal disclaimer.

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(22) **Filed:** Apr. 7, 2003

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 09/874,117, filed on Jun. 4, 2001, now Pat. No. 6,585,764, which is a continuation of application No. 09/061,568, filed on Apr. 16, 1998, now Pat. No. 6,273,913.

(60) Provisional application No. 60/044,692, filed on Apr. 18, 1997.

(51) **Int. Cl.** A61F 2/06

(52) **U.S. Cl.** 623/1.42

(58) **Field of Search** 623/1.15, 1.39, 623/1.42, 1.4; 427/2.1-2.31

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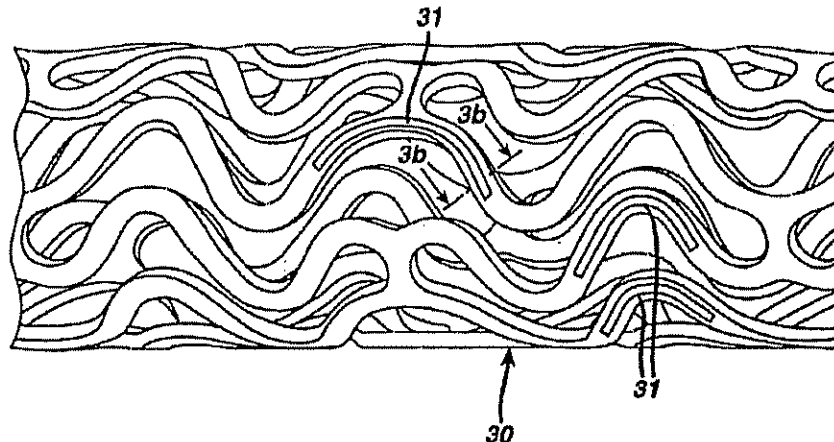
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Primary Examiner—Suzette J. Jackson

(57) **ABSTRACT**

Delivery of rapamycin locally, particularly from an intra-vascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

6 Claims, 2 Drawing Sheets



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FIG. 1

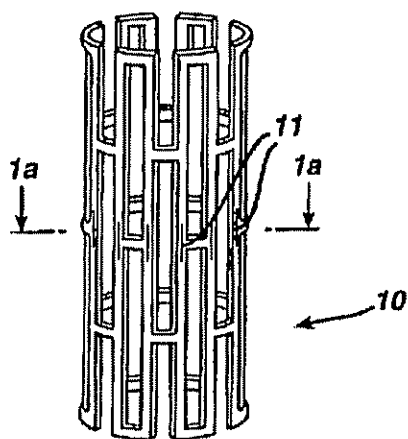


FIG. 1a

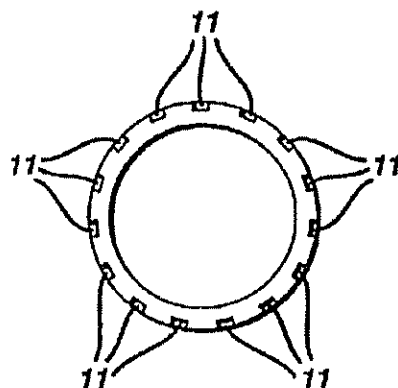


FIG. 2a

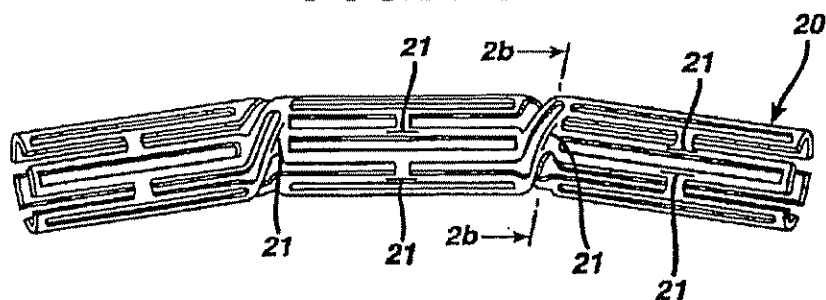
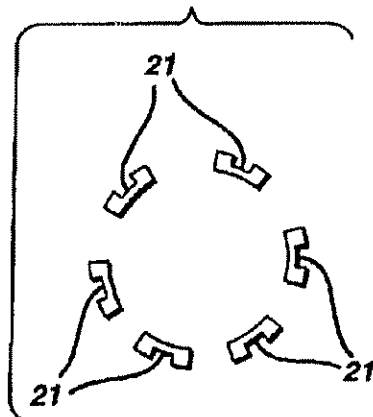


FIG. 2b



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FIG. 3a

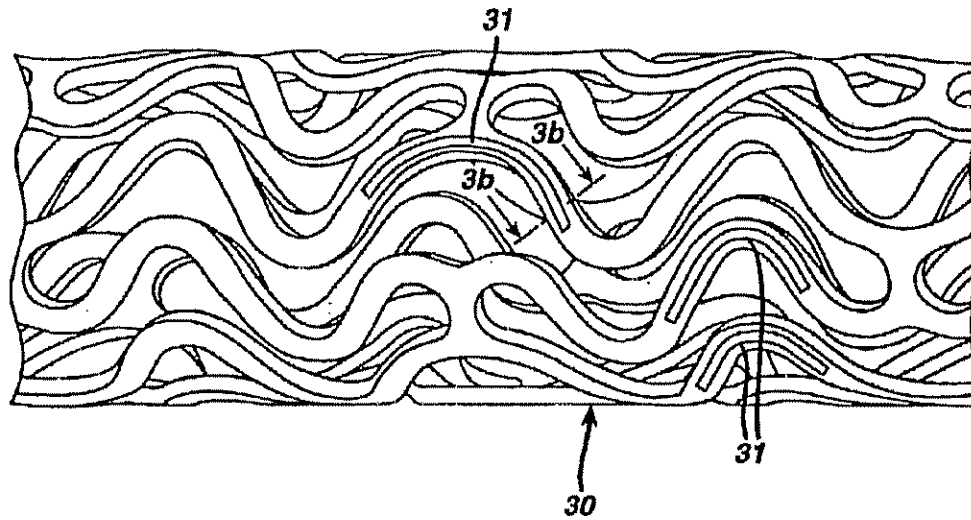


FIG. 3b

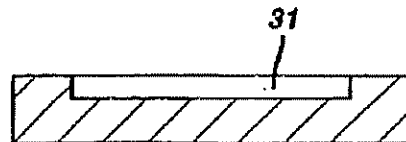
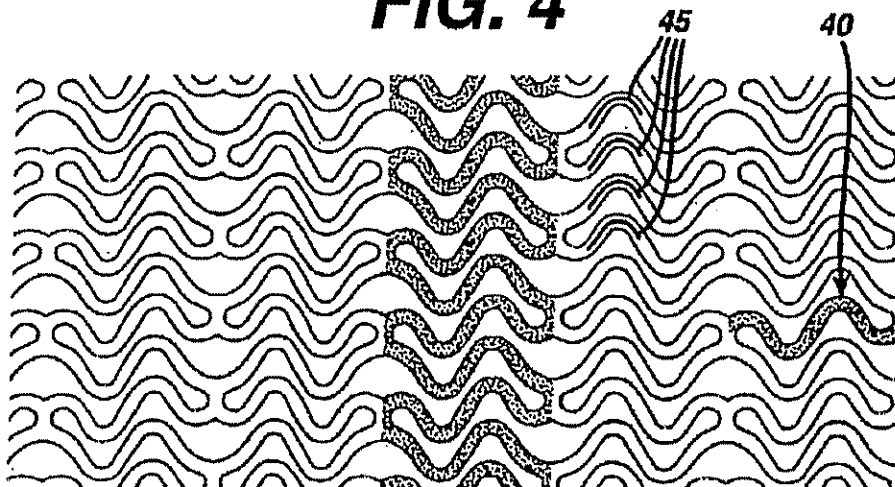


FIG. 4



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**STENT CONTAINING RAPAMYCIN OR ITS
ANALOGS USING A MODIFIED STENT**

Continuation of prior application Ser. No.: 09/874,117, filed Jun. 4, 2001, now U.S. Pat. No. 6,585,764 which is a continuation of Ser. No. 09/061,568 filed Apr. 16, 1998, now U.S. Pat. No. 6,273,913; which claim the benefit of U.S. Provisional Application No. 60/044,692, filed Apr. 18, 1997.

FIELD OF THE INVENTION

Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

BACKGROUND OF THE INVENTION

Re-narrowing (restenosis) of an atherosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10–50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft. While the exact hormonal and cellular processes promoting restenosis are still being determined, our present understanding is that the process of PTCA, besides opening the atherosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC). In response to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3–6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow.

Several recent experimental approaches to preventing SMC proliferation have shown promise although the mechanisms for most agents employed are still unclear. Heparin is the best known and characterized agent causing inhibition of SMC proliferation both in vitro and in animal models of balloon angioplasty-mediated injury. The mechanism of SMC inhibition with heparin is still not known but may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes c-fos and c-myc, 2) reduced cellular production of tissue plasminogen activator; are 3) binding and dequstration of growth regulatory factors such as fibrovalent growth factor (FGF).

Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers, angiotensin converting enzyme inhibitors (captopril, cilazapril), cyclosporin A, trapidil (an antianginal, antiplatelet agent), terbinafine (antifungal), colchicine and taxol (antitubulin antiproliferatives), and c-myc and c-myb antisense oligonucleotides.

Additionally, a goat antibody to the SMC mitogen platelet derived growth factor (PDGF) has been shown to be effective in reducing myointimal thickening in a rat model of balloon angioplasty injury, thereby implicating PDGF directly in the etiology of restenosis. Thus, while no therapy has as yet proven successful clinically in preventing restenosis after angioplasty, the in vivo experimental success of several agents known to inhibit SMC growth suggests that

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these agents as a class have the capacity to prevent clinical restenosis and deserve careful evaluation in humans.

Coronary heart disease is the major cause of death in men over the age of 40 and in women over the age of fifty in the western world. Most coronary artery-related deaths are due to atherosclerosis. Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500,000–600,000 deaths in the United States annually. To arrest the disease process and prevent the more advanced disease states in which the cardiac muscle itself is compromised, direct intervention has been employed via percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG).

PTCA is a procedure in which a small balloon-tipped catheter is passed down a narrowed coronary artery and then expanded to re-open the artery. It is currently performed in approximately 250,000–300,000 patients each year. The major advantage of this therapy is that patients in which the procedure is successful need not undergo the more invasive surgical procedure of coronary artery bypass graft. A major difficulty with PTCA is the problem of post-angioplasty closure of the vessel, both immediately after PTCA (acute reocclusion) and in the long term (restenosis).

The mechanism of acute reocclusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus. Recently, intravascular stents have been examined as a means of preventing acute reclosure after PTCA.

Restenosis (chronic reclosure) after angioplasty is a more gradual process than acute reocclusion: 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty. While the exact mechanism for restenosis is still under active investigation, the general aspects of the restenosis process have been identified:

In the normal arterial wall, smooth muscle cells (SMC) proliferate at a low rate (<0.1%/day; ref). SMC in vessel wall exists in a 'contractile' phenotype characterized by 80–90% of the cell cytoplasmic volume occupied by the contractile apparatus. Endoplasmic reticulum, golgi bodies, and free ribosomes are few and located in the perinuclear region. Extracellular matrix surrounds SMC and is rich in heparin-like glycosaminoglycans which are believed to be responsible for maintaining SMC in the contractile phenotypic state.

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the arterial wall become injured. Cell derived growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), etc. released from platelets (i.e., PDGF) adhering to the damaged arterial luminal surface, invading macrophages and/or leukocytes, or directly from SMC (i.e., bFGF) provoke a proliferation and migratory response in medial SMC. These cells undergo a phenotypic change from the contractile phenotype to a 'synthetic' phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum, golgi and free ribosomes. Proliferation/migration usually begins within 1–2 days post-injury and peaks at 2 days in the media, rapidly declining thereafter (Campbell et al., In: *Vascular Smooth Muscle Cells in Culture*, Campbell, J. H. and Campbell, G. R., Eds, CRC Press, Boca Ration, 1987, pp. 39–55; Clowes, A. W. and Schwartz, S. M., *Circ. Res.* 56:139–145, 1985).

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Finally, daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate. Proliferation and migration continues until the damaged luminal endothelial layer regenerates at which time proliferation ceases within the intima, usually within 7-14 days postinjury. The remaining increase in intimal thickening which occurs over the next 3-6 months is due to an increase in extracellular matrix rather than cell number. Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response. (Liu et al., *Circulation*, 79:1374-1387, 1989).

Patients with symptomatic reocclusion require either repeat PTCA or CABG. Because 30-50% of patients undergoing PTCA will experience restenosis, restenosis has clearly limited the success of PTCA as a therapeutic approach to, coronary artery disease. Because SMC proliferation and migration are intimately involved with the pathophysiological response to arterial injury, prevention of SMC proliferation and migration represents a target for pharmacological intervention in the prevention of restenosis.

SUMMARY OF THE INVENTION

Novel Features and Applications to Stent Technology

Currently, attempts to improve the clinical performance of stents have involved some variation of either applying a coating to the metal, attaching a covering or membrane, or embedding material on the surface via ion bombardment. A stent designed to include reservoirs is a new approach which offers several important advantages over existing technologies.

Local Drug Delivery from a Stent to Inhibit Restenosis

In this application, it is desired to deliver a therapeutic agent to the site of arterial injury. The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent. The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks, and be as thin as possible so as to minimize the increase in profile. In addition, the coating material should not contribute to any adverse response by the body (i.e., should be non-thrombogenic, non-inflammatory, etc.). To date, the ideal coating material has not been developed for this application.

An alternative would be to design the stent to contain reservoirs which could be loaded with the drug. A coating or membrane of biocompatible material could be applied over the reservoirs which would control the diffusion of the drug from the reservoirs to the artery wall.

One advantage of this system is that the properties of the coating can be optimized for achieving superior biocompatibility and adhesion properties, without the addition requirement of being able to load and release the drug. The size, shape, position, and number of reservoirs can be used to control the amount of drug, and therefore the dose delivered.

DESCRIPTION OF THE DRAWINGS

The invention will be better understood in connection with the following figures in which

FIGS. 1 and 1A are top views and section views of a stent containing reservoirs as described in the present invention;

FIGS. 2a and 2b are similar views of an alternate embodiment of the stent with open ends;

FIGS. 3a and 3b are further alternate figures of a device containing a grooved reservoir; and

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FIG. 4 is a layout view of a device containing a reservoir as in FIG. 3.

DETAILED DESCRIPTION OF THE INVENTION

Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents. Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty. The calcium antagonists have also been unsuccessful in preventing restenosis, although they are still under study. Other agents currently under study include thromboxane inhibitors, prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al., 42 *Ann. Rev. Med.*, 127-132 (1991); Popma et al., 84 *Circulation*, 1426-1436 (1991)).

Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements, thromboxane receptor antagonists, cholesterol lowering agents, and serotonin antagonists has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Franklin, S. M. and Faxon, D. P., 4 *Coronary Artery Disease*, 232-242 (1993); Serruys, P. W. et al., 88 *Circulation*, (part 1) 1588-1601, (1993).

Conversely, stents have proven useful in preventing reducing the proliferation of restenosis. Stents, such as the stent 10 seen in layout in FIG. 4, balloon-expandable slotted metal tubes (usually but not limited to stainless steel), which when expanded within the lumen of an angioplastied coronary artery, provide structural support to the arterial wall. This support is helpful in maintaining an open path for blood flow. In two randomized clinical trials, stents were shown to increase angiographic success after PTCA, increase the stenosed blood vessel lumen and to reduce the lesion recurrence at 6 months (Serruys et al., 331 *New Eng Jour. Med.*, 495, (1994); Fischman et al., 331 *New Eng Jour. Med.*, 496-501 (1994). Additionally, in a preliminary trial, heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Additionally, heparin coating appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 93 *Circulation*, 412-422, (1996). Thus, 1) sustained mechanical expansion of a stenosed coronary artery has been shown to provide some measure of restenosis prevention, and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs to local, injured tissue off the surface of the stent.

Numerous agents are being actively studied as antiproliferative agents for use in restenosis and have shown some activity in experimental animal models. These include: heparin and heparin fragments (Clowes and Karnovsky, 265 *Nature*, 25-626, (1977); Guyton, J. R. et al. 46 *Circ. Res.*, 625-634, (1980); Clowes, A. W. and Clowes, M. M., 52 *Lab.*

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Of particular interest in rapamycin. Rapamycin is a macrolide antibiotic which blocks IL-2-mediated T-cell proliferation and possesses antiinflammatory activity. While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G₁ to S phase progression of T-cells through the cell cycle by inhibiting specific cell cyclins and cyclin-dependent protein kinases (Siekierka, *Immunol. Res.* 13: 110-116, 1994). The antiproliferative action of rapamycin is not limited to T-cells; Marx et al (*Circ Res* 76:412-417, 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC in vitro while Poon et al have shown the rat, porcine, and human SMC migratin can also be inhibited by rapamycin (*J Clin Invest* 98: 2277-2283, 1996). Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response. In fact, the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in a rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al., *Transplantation* 55:1409-1418, 1993; Gallo et al., in press, (1997)). These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis.

Although the ideal agent for restenosis has not yet been identified, some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury, including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications. Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of SMC combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

Experiments

Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression.

Delivery Methods:

These can vary:

Local delivery of such agents (rapamycin) from the struts of a stent, from a stent graft, grafts, stent cover or sheath.

Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft

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or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein.

or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e.g. vapour deposition methods such as rf-plasma polymerization) and combinations thereof.

Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake

Extravascular delivery by the pericardial route

Extravascular delivery by the advential application of sustained release formulations.

Uses: for inhibition of cell proliferation to prevent neointimal proliferation and restenosis.

prevention of tumor expansion from stents

prevent ingrowth of tissue into catheters and shunts inducing their failure.

1. Experimental Stent Delivery Method—Delivery from Polymer Matrix:

Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0.001 weight % to 30 weight % of drug. Polymers are biocompatible (i.e., not elicit any negative tissue reaction or promote mural thrombus formation) and degradable, such as lactone-based polyesters or copolyesters, e.g., polylactide, polycaprolactone-glycolide, polyorthoesters, polyanhydrides; polyaminoacids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, e.g., PEO-PLLA, or blends thereof. Nonabsorbable biocompatible polymers are also suitable candidates. Polymers such as polydimethylsiloxane; poly(ethylene-vinylacetate); acrylate based polymers or copolymers, e.g., poly(hydroxyethyl methacrylate, polyvinyl pyrrolidone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters.

Polymer/drug mixture is applied to the surfaces of the stent by either dip-coating, or spray coating, or brush coating or dip/spin coating or combinations thereof, and the solvent allowed to evaporate to leave a film with entrapped rapamycin.

2. Experimental Stent Delivery Method—Delivery from Microporous Depots in Stent Through a Polymer Membrane Coating:

Stent, whose body has been modified to contain micropores or channels is dipped into a solution of Rapamycin, range 0.001 wt % to saturated, in organic solvent such as acetone or methylene chloride, for sufficient time to allow solution to permeate into the pores. (The dipping solution can also be compressed to improve the loading efficiency.) After solvent has been allowed to evaporate, the stent is dipped briefly in fresh solvent to remove excess surface bound drug. A solution of polymer, chosen from any identified in the first experimental method, is applied to the stent as detailed above. This outerlayer of polymer will act as diffusion-controller for release of drug.

3. Experimental Stent Delivery Method—Delivery via Lysis of a Covalent Drug Tether

Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization. Covalent bonds such as ester, amides or anhydrides may be suitable for this.

4. Experimental Method—Pericardial Delivery

A: Polymeric Sheet Rapamycin is combined at concentration range previously highlighted, with a degradable

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polymer such as poly(caprolactone-glycolide) or non-degradable polymer, e.g., polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10μ to 1000μ . The resulting sheet can be wrapped perivascularly on the target vessel. Preference would be for the absorbable polymer.

B: Conformal Coating: Rapamycin is combined with a polymer that has a melting temperature just above 37°C , range 40° – 45°C . Mixture is applied in a molten state to the external side of the target vessel. Upon cooling to body temperature the mixture solidifies conformally to the vessel wall. Both non-degradable and absorbable biocompatible polymers are suitable.

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin. As seen in FIGS. 1a, 2a and 3a, any stent strut 10, 20, 30 can be modified to have a certain reservoir or channel 11, 21, 31. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. FIG. 4 shows a stent 40 with a reservoir 45 created at the apex of a flexible strut. Of course, this reservoir 45 is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents.

In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must be kept at a size of about $0.0005''$ to about $0.003''$. Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

These and other concepts will be disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be perceived to fall within the scope of the invention which is to be realized from the attached claims and their equivalents.

What is claimed is:

1. A stent having a coating containing rapamycin or its analogs, wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0.0001% to 30% , said stent further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said coating applied to said strut, and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top, and said channel smaller in all dimensions than said strut, said channel containing a reservoir of said rapamycin containing coating applied therein.

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2. A stent having a coating containing rapamycin or its analogs, wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0.0001% to 30% , wherein the coating is a polymer, said stent further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said coating applied to said strut, and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top, and said channel smaller in all dimensions than said strut, said channel containing a reservoir of said rapamycin containing coating applied therein.

3. A stent containing a polymer and rapamycin or its analogs wherein said rapamycin or its analogs are contained in a therapeutically beneficial amount to combat restenosis, said stent further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said coating applied to said strut, and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top, and said channel smaller in all dimensions than said strut, said channel containing a reservoir of said rapamycin containing coating applied therein.

4. A stent having a coating containing rapamycin or its analogs, wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0.0001% to 30% , said stent further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said coating applied to said struts.

5. A stent having a coating containing rapamycin or its analogs, wherein said rapamycin or said analogs are contained in the coating at a weight percentage of 0.0001% to 30% , wherein the coating is a polymer, said stent further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said coating applied to said struts.

6. A stent containing a polymer and rapamycin or its analogs wherein said rapamycin or its analogs are contained in a therapeutically beneficial amount to combat restenosis, said stent further comprising:

a generally thin walled cylinder, said cylinder containing a plurality of generally solid struts, said coating applied to said struts.

* * * * *

Exhibit C



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(12) **United States Patent**
Falotico et al.

(10) **Patent No.:** US 6,776,796 B2
(45) **Date of Patent:** Aug. 17, 2004

(54) **ANTHINFLAMMATORY DRUG AND DELIVERY DEVICE**

(75) Inventors: Robert Falotico, Belle Mead, NJ (US); Gregory A. Kopia, Neshanic, NJ (US); Gerard H. Llanos, Stewartsville, NJ (US); John Sieklerka, Towaco, NJ (US); Andrew J. Carter, Portland, OR (US)

(73) Assignee: Cordis Corporation, Miami Lakes, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 129 days.

(21) Appl. No.: 09/850,232

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(65) **Prior Publication Data**

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Related U.S. Application Data

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(51) **Int. Cl.**⁷ A61F 2/06

(52) **U.S. Cl.** 623/1.46

(58) **Field of Search** 623/1.42, 1.43, 623/1.44, 1.45, 1.46

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Primary Examiner—Manuel Mendez

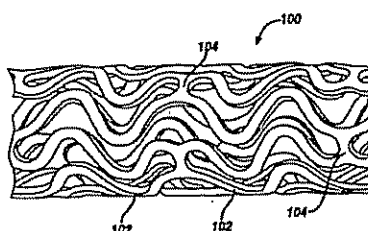
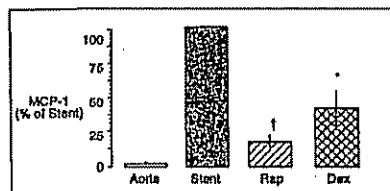
Assistant Examiner—Mark K. Han

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(57) **ABSTRACT**

A drug and drug delivery system may be utilized in the treatment of vascular disease. A local delivery system is coated with rapamycin or other suitable drug, agent or compound and delivered intraluminally for the treatment and prevention of neointimal hyperplasia following percutaneous transluminal coronary angiography. The local delivery of the drugs or agents provides for increased effectiveness and lower systemic toxicity.

11 Claims, 2 Drawing Sheets



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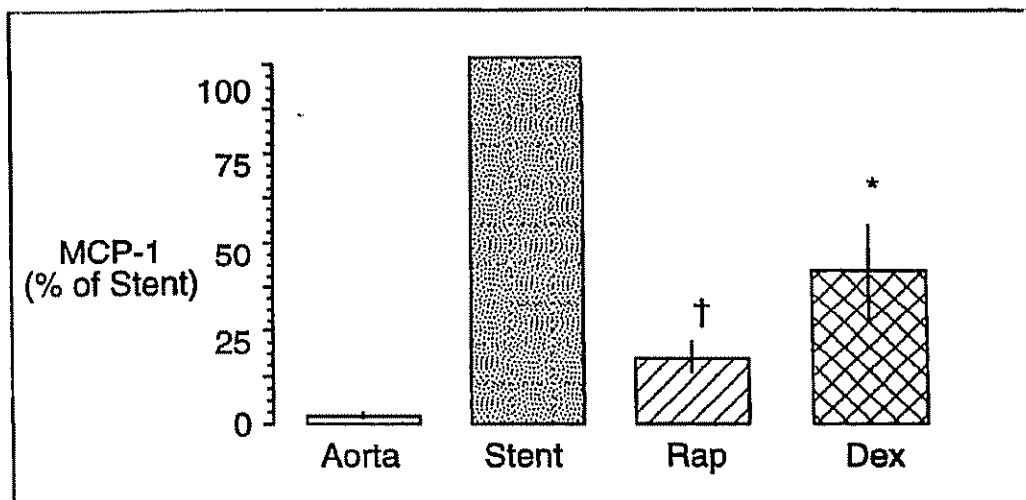
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FIG. 1



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FIG. 2

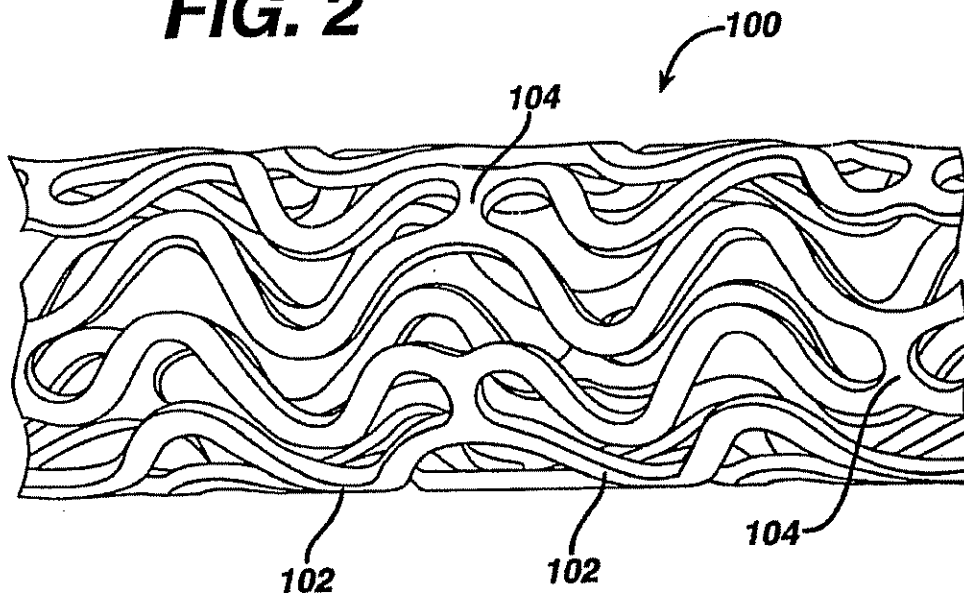
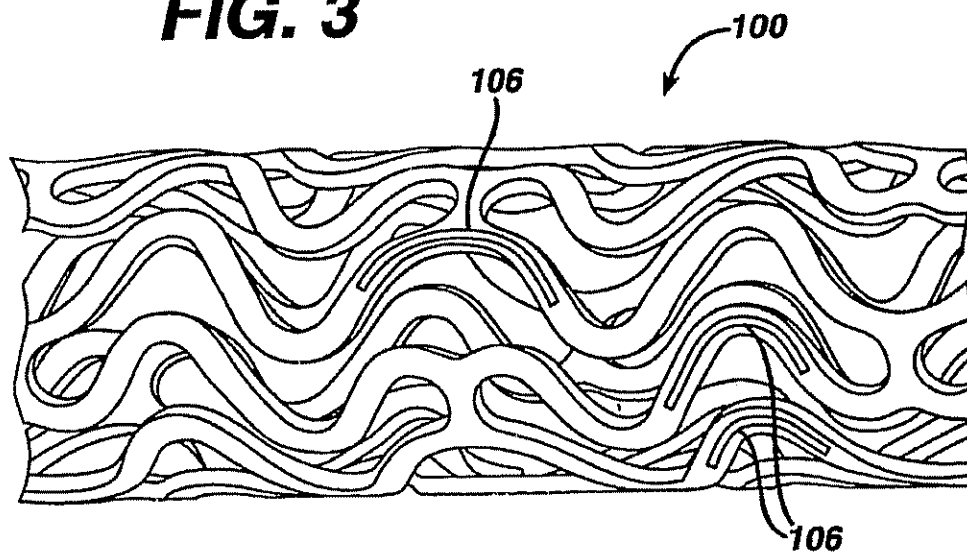


FIG. 3



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ANTIINFLAMMATORY DRUG AND DELIVERY DEVICE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part application of U.S. application Ser. No. 09/575,480, filed on May 19, 2000 which claims the benefit of U.S. Provisional Application No. 60/204,417, filed May 12, 2000 and claims the benefit of, U.S. Provisional Application No. 60/262,614, filed Jan. 18, 2001, U.S. Provisional Application No. 60/262,461, filed Jan. 18, 2001, U.S. Provisional Application No. 60/263,806, filed Jan. 24, 2001 and U.S. Provisional Application No. 60/263,979, filed Jan. 25, 2001.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to drugs and drug delivery systems for the prevention and treatment of vascular disease, and more particularly to drugs and drug delivery systems for the prevention and treatment of neointimal hyperplasia.

2 Discussion of the Related Art

Many individuals suffer from circulatory disease caused by a progressive blockage of the blood vessels that perfuse the heart and other major organs with nutrients. More severe blockage of blood vessels in such individuals often leads to hypertension, ischemic injury, stroke, or myocardial infarction. Atherosclerotic lesions, which limit or obstruct coronary blood flow, are the major cause of ischemic heart disease. Percutaneous transluminal coronary angioplasty is a medical procedure whose purpose is to increase blood flow through an artery. Percutaneous transluminal coronary angioplasty is the predominant treatment for coronary vessel stenosis. The increasing use of this procedure is attributable to its relatively high success rate and its minimal invasiveness compared with coronary bypass surgery. A limitation associated with percutaneous transluminal coronary angioplasty is the abrupt closure of the vessel which may occur immediately after the procedure and restenosis which occurs gradually following the procedure. Additionally, restenosis is a chronic problem in patients who have undergone saphenous vein bypass grafting. The mechanism of acute occlusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets and fibrin along the damaged length of the newly opened blood vessel.

Restenosis after percutaneous transluminal coronary angioplasty is a more gradual process initiated by vascular injury. Multiple processes, including thrombosis, inflammation, growth factor and cytokine release, cell proliferation, cell migration and extracellular matrix synthesis each contribute to the restenotic process.

While the exact mechanism of restenosis is not completely understood, the general aspects of the restenosis process have been identified. In the normal arterial wall, smooth muscle cells proliferate at a low rate, approximately less than 0.1 percent per day. Smooth muscle cells in the vessel walls exist in a contractile phenotype characterized by eighty to ninety percent of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, Golgi, and free ribosomes are few and are located in the perinuclear region. Extracellular matrix surrounds the smooth muscle cells and is rich in heparin-like glycosaminoglycans which are believed to be responsible for maintaining smooth muscle cells in the contractile phenotypic state (Campbell and Campbell, 1985).

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Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the vessel wall become injured, initiating a thrombotic and inflammatory response. Cell derived growth factors such as platelet derived growth factor, fibroblast growth factor, epidermal growth factor, thrombin, etc., released from platelets, invading macrophages and/or leukocytes, or directly from the smooth muscle cells provoke proliferative and migratory responses in medial smooth muscle cells. These cells undergo a change from the contractile phenotype to a synthetic phenotype characterized by only a few contractile filament bundles, extensive rough endoplasmic reticulum, Golgi and free ribosomes. Proliferation/migration usually begins within one to two days post-injury and peaks several days thereafter (Campbell and Campbell, 1987; Clowes and Schwartz, 1985).

Daughter cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate and secrete significant amounts of extracellular matrix proteins. Proliferation, migration and extracellular matrix synthesis continue until the damaged endothelial layer is repaired at which time proliferation slows within the intima, usually within seven to fourteen days post-injury. The newly formed tissue is called neointima. The further vascular narrowing that occurs over the next three to six months is due primarily to negative or constrictive remodeling.

Simultaneous with local proliferation and migration, inflammatory cells invade the site of vascular injury. Within three to seven days post-injury, inflammatory cells have migrated to the deeper layers of the vessel wall. In animal models employing either balloon injury or stent implantation, inflammatory cells may persist at the site of vascular injury for at least thirty days (Tanaka et al., 1993; Edelman et al., 1998). Inflammatory cells therefore are present and may contribute to both the acute and chronic phases of restenosis.

Numerous agents have been examined for presumed anti-proliferative actions in restenosis and have shown some activity in experimental animal models. Some of the agents which have been shown to successfully reduce the extent of intimal hyperplasia in animal models include: heparin and heparin fragments (Clowes, A. W. and Karnovsky M., *Nature* 265: 25-26, 1977; Guyton, J. R. et al., *Circ. Res.*, 46: 625-634, 1980; Clowes, A. W. and Clowes, M. M., *Lab. Invest.* 52: 611-616, 1985; Clowes, A. W. and Clowes, M. M., *Circ. Res.* 58: 839-845, 1986; Majesky et al., *Circ. Res.* 61: 296-300, 1987; Snow et al., *Am. J. Pathol.* 137: 313-330, 1990; Okada, T. et al., *Neurosurgery* 25: 92-98, 1989), colchicine (Currier, J. W. et al., *Circ.* 80: 11-66, 1989), taxol (Sollot, S. J. et al., *J. Clin. Invest.* 95: 1869-1876, 1995), angiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., *Science*, 245: 186-188, 1989), angiotensin II receptor antagonists (Lundergan, C. F. et al., *Am. J. Cardiol.* 17(Suppl. B):132B-136B, 1991), cyclosporin A (Jonasson, L. et al., *Proc. Natl. Acad. Sci.*, 85: 2303, 1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., *Science* 253: 1129-1132, 1991), terbinafine (Nemecek, G. M. et al., *J. Pharmacol. Exp. Thera.* 248: 1167-1174, 1989), trapidil (Liu, M. W. et al., *Circ.* 81: 1089-1093, 1990), tranilast (Fukuyama, J. et al., *Eur. J. Pharmacol.* 318: 327-332, 1996), interferon-gamma (Hansson, G. K. and Holm, J., *Circ.* 84:1266-1272, 1991), rapamycin (Marx, S. O. et al., *Circ. Res.* 76: 412417, 1995), corticosteroids (Colburn, M. D. et al., *J. Vasc. Surg.* 15: 510-518, 1992), see also Berk, B. C. et al., *J. Am. Coll. Cardiol.* 17: 111 B-117B, 1991), ionizing radiation (Weinberger, J. et al., *Int. J. Rad. Onc. Biol. Phys.* 36: 767-775, 1996), fusion toxins (Farb, A. et al.,

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Circ. Res. 80: 542-550, 1997) antisense oligonucleotides (Simons, M. et al., Nature 359: 67-70, 1992) and gene vectors (Chang, M. W. et al., J. Clin. Invest. 96: 2260-2268, 1995). Anti-proliferative effects on smooth muscle cells in vitro have been demonstrated for many of these agents, including heparin and heparin conjugates, taxol, tranilast, colchicine, ACE inhibitors, fusion toxins, antisense oligonucleotides, rapamycin and ionizing radiation. Thus, agents with diverse mechanisms of smooth muscle cell inhibition may have therapeutic utility in reducing intimal hyperplasia.

However, in contrast to animal models, attempts in human angioplasty patients to prevent restenosis by systemic pharmacologic means have thus far been unsuccessful. Neither aspirin-dipyridamole, ticlopidine, anti-coagulant therapy (acute heparin, chronic warfarin, hirudin or hirulog), thromboxane receptor antagonism nor steroids have been effective in preventing restenosis, although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty (Mak and Topol, 1997; Lang et al., 1991; Popma et al., 1991). The platelet GP IIb/IIIa receptor, antagonist, Reopro is still under study but has not shown promising results for the reduction in restenosis following angioplasty and stenting. Other agents, which have also been unsuccessful in the prevention of restenosis, include the calcium channel antagonists, prostacyclin mimetics, angiotensin converting enzyme inhibitors, serotonin receptor antagonists, and anti-proliferative agents. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; anti-proliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Mak and Topol, 1997; Lang et al., 1991; Popma et al., 1991).

Additional clinical trials in which the effectiveness for preventing restenosis utilizing dietary fish oil supplements or cholesterol lowering agents has been examined showing either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Mak and Topol, 1997; Franklin and Faxon, 1993; Serruys, P. W. et al., 1993). Recent observations suggest that the antilipid/antioxidant agent, probucol may be useful in preventing restenosis but this work requires confirmation (Tardif et al., 1997; Yokoi, et al., 1997). Probuco is presently not approved for use in the United States and a thirty-day pretreatment period would preclude its use in emergency angioplasty. Additionally, the application of ionizing radiation has shown significant promise in reducing or preventing restenosis after angioplasty in patients with stents (Teirstein et al., 1997). Currently, however, the most effective treatments for restenosis are repeat angioplasty, atherectomy or coronary artery bypass grafting, because no therapeutic agents currently have Food and Drug Administration approval for use for the prevention of post-angioplasty restenosis.

Unlike systemic pharmacologic therapy, stents have proven effective in significantly reducing restenosis. Typically, stents are balloon-expandable slotted metal tubes (usually, but not limited to, stainless steel), which, when expanded within the lumen of an angioplastied coronary artery, provide structural support through rigid scaffolding to the arterial wall. This support is helpful in maintaining vessel lumen patency. In two randomized clinical trials, stents increased angiographic success after percutaneous transluminal coronary angioplasty, by increasing minimal lumen diameter and reducing, but not eliminating, the inci-

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dence of restenosis at six months (Serruys et al., 1994; Fischman et al., 1994).

Additionally, the heparin coating of stents appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 1996). Thus, sustained mechanical expansion of a stenosed coronary artery with a stent has been shown to provide some measure of restenosis prevention, and the coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs locally, at the site of injured tissue.

Accordingly, there exists a need for effective drugs and drug delivery systems for the effective prevention and treatment of neointimal thickening that occurs after percutaneous transluminal coronary angioplasty and stent implantation.

SUMMARY OF THE INVENTION

The drugs and drug delivery systems of the present invention provide a means for overcoming the difficulties associated with the methods and devices currently in use as briefly described above.

In accordance with one aspect, the present invention is directed to a method for the treatment of intimal hyperplasia in vessel walls. The method comprises the controlled delivery, by release from an intraluminal medical device, of an anti-inflammatory agent in therapeutic dosage amounts.

In accordance with another aspect, the present invention is directed to a drug delivery device. The drug delivery device comprises an intraluminal medical device and a therapeutic dosage of an agent releasably affixed to the intraluminal medical device for the treatment of inflammation caused by injury.

In accordance with another aspect, the present invention is directed to a method for the treatment of inflammation in vessel walls. The method comprises the controlled delivery, by release from an intraluminal medical device, of an anti-inflammatory agent in therapeutic dosage amounts.

The drugs and drug delivery systems of the present invention utilize a stent or graft in combination with rapamycin or other drugs/agents/compounds to prevent and treat neointimal hyperplasia, i.e. restenosis, following percutaneous transluminal coronary angioplasty and stent implantation. It has been determined that rapamycin functions to inhibit smooth muscle cell proliferation through a number of mechanisms. It has also been determined that rapamycin eluting stent coatings produce superior effects in humans, when compared to animals, with respect to the magnitude and duration of the reduction in neointimal hyperplasia. Rapamycin administration from a local delivery platform also produces an anti-inflammatory effect in the vessel wall that is distinct from and complimentary to its smooth muscle cell anti-proliferative effect. In addition, it has also been demonstrated that rapamycin inhibits constrictive vascular remodeling in humans.

Other drugs, agents or compounds which mimic certain actions of rapamycin may also be utilized in combination with local delivery systems or platforms.

The local administration of drugs, agents or compounds to stented vessels have the additional therapeutic benefit of higher tissue concentration than that which would be achievable through the systemic administration of the same drugs, agents or compounds. Other benefits include reduced systemic toxicity, single treatment, and ease of administration. An additional benefit of a local delivery device and drug,

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agent or compound therapy may be to reduce the dose of the therapeutic drugs, agents or compounds and thus limit their toxicity, while still achieving a reduction in restenosis.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other features and advantages of the invention will be apparent from the following, more particular description of preferred embodiments of the invention, as illustrated in the accompanying drawings.

FIG. 1 is a chart indicating the effectiveness of rapamycin as an anti-inflammatory relative to other anti-inflammatories.

FIG. 2 is a view along the length of a stent (ends not shown) prior to expansion showing the exterior surface of the stent and the characteristic banding pattern.

FIG. 3 is a perspective view of the stent of FIG. 1 having reservoirs in accordance with the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As stated above, the proliferation of vascular smooth muscle cells in response to mitogenic stimuli that are released during balloon angioplasty and stent implantation is the primary cause of neointimal hyperplasia. Excessive neointimal hyperplasia can often lead to impairment of blood flow, cardiac ischemia and the need for a repeat intervention in selected patients in high risk treatment groups. Yet repeat revascularization incurs risk of patient morbidity and mortality while adding significantly to the cost of health care. Given the widespread use of stents in interventional practice, there is a clear need for safe and effective inhibitors of neointimal hyperplasia.

Rapamycin is a macrocyclic triene antibiotic produced by streptomyces hygroscopicus as disclosed in U.S. Pat. No. 3,929,992. It has been found that rapamycin inhibits the proliferation of vascular smooth muscle cells in vivo. Accordingly, rapamycin may be utilized in treating intimal smooth muscle cell hyperplasia, restenosis and vascular occlusion in a mammal, particularly following either biologically or mechanically mediated vascular injury, or under conditions that would predispose a mammal to suffering such a vascular injury. Rapamycin functions to inhibit smooth muscle cell proliferation and does not interfere with the re-endothelialization of the vessel walls.

Rapamycin functions to inhibit smooth muscle cell proliferation through a number of mechanisms. In addition, rapamycin reduces the other effects caused by vascular injury, for example, inflammation. The operation and various functions of rapamycin are described in detail below. Rapamycin as used throughout this application shall include rapamycin, rapamycin analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

Rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during angioplasty. Inhibition of growth factor and cytokine mediated smooth muscle proliferation at the late G1 phase of the cell cycle is believed to be the dominant mechanism of action of rapamycin. However, rapamycin is also known to prevent T-cell proliferation and differentiation when administered systemically. This is the basis for its immunosuppressive activity and its ability to prevent graft rejection.

The molecular events that are responsible for the actions of rapamycin, a known anti-proliferative, which acts to

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reduce the magnitude and duration of neointimal hyperplasia, are still being elucidated. It is known, however, that rapamycin enters cells and binds to a high-affinity cytosolic protein called FKBP12. The complex of rapamycin and FKBP12 in turn binds to and inhibits a phosphoinositide (PI)-3 kinase called the "mammalian Target of Rapamycin" or TOR. TOR is a protein kinase that plays a key role in mediating the downstream signaling events associated with mitogenic growth factors and cytokines in smooth muscle cells and T lymphocytes. These events include phosphorylation of p27, phosphorylation of p70 s6 kinase and phosphorylation of 4BP-1, an important regulator of protein translation.

It is recognized that rapamycin reduces restenosis by inhibiting neointimal hyperplasia. However, there is evidence that rapamycin may also inhibit the other major component of restenosis, namely, negative remodeling. Remodeling is a process whose mechanism is not clearly understood but which results in shrinkage of the external elastic lamina and reduction in luminal area over time, generally a period of approximately three to six months in humans.

Negative or constrictive vascular remodeling may be quantified angiographically as the percent diameter stenosis at the lesion site where there is no stent to obstruct the process. If late lumen loss is abolished in-lesion, it may be inferred that negative remodeling has been inhibited. Another method of determining the degree of remodeling involves measuring in-lesion external elastic lamina area using intravascular ultrasound (IVUS). Intravascular ultrasound is a technique that can image the external elastic lamina as well as the vascular lumen. Changes in the external elastic lamina proximal and distal to the stent from the post-procedural timepoint to four-month and twelve-month follow-ups are reflective of remodeling changes.

Evidence that rapamycin exerts an effect on remodeling comes from human implant studies with rapamycin coated stents showing a very low degree of restenosis in-lesion as well as in-stent. In-lesion parameters are usually measured approximately five millimeters on either side of the stent i.e. proximal and distal. Since the stent is not present to control remodeling in these zones which are still affected by balloon expansion, it may be inferred that rapamycin is preventing vascular remodeling.

The data in Table 1 below illustrate that in-lesion percent diameter stenosis remains low in the rapamycin treated groups, even at twelve months. Accordingly, these results support the hypothesis that rapamycin reduces remodeling.

TABLE 1.0

Coating Group	Angiographic In-Lesion Percent Diameter Stenosis (% mean \pm SD and "n" in Patients Who Received a Rapamycin-Coated Stent)		
	Post Placement	4-6 month Follow Up	12 month Follow Up
Brazil	10.6 \pm 5.7 (30)	13.6 \pm 8.6 (30)	22.3 \pm 7.2 (15)
Netherlands	14.7 \pm 8.8	22.4 \pm 6.4	—

Additional evidence supporting a reduction in negative remodeling with rapamycin comes from intravascular ultrasound data that was obtained from a first-in-man clinical program as illustrated in Table 2 below.

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TABLE 2.0

Matched IVUS data in Patients Who Received a Rapamycin-Coated Stent

IVUS Parameter	Post (n=)	4-Month Follow-Up (n=)	12-Month Follow-Up (n=)
Mean proximal vessel area (mm ²)	16.53 ± 3.53 (27)	16.31 ± 4.36 (28)	13.96 ± 2.26 (13)
Mean distal vessel area (mm ²)	13.12 ± 3.68 (26)	13.53 ± 4.17 (26)	12.49 ± 3.25 (14)

The data illustrated that there is minimal loss of vessel area proximally or distally which indicates that inhibition of negative remodeling has occurred in vessels treated with rapamycin-coated stents.

Other than the stent itself, there have been no effective solutions to the problem of vascular remodeling. Accordingly, rapamycin may represent a biological approach to controlling the vascular remodeling phenomenon.

It may be hypothesized that rapamycin acts to reduce negative remodeling in several ways. By specifically blocking the proliferation of fibroblasts in the vascular wall in response to injury, rapamycin may reduce the formation of vascular scar tissue. Rapamycin may also affect the translation of key proteins involved in collagen formation or metabolism.

Rapamycin used in this context includes rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

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In a preferred embodiment, the rapamycin is delivered by a local delivery device to control negative remodeling of an arterial segment after balloon angioplasty as a means of reducing or preventing restenosis. While any delivery device may be utilized, it is preferred that the delivery device comprises a stent that includes a coating or sheath which elutes or releases rapamycin. The delivery system for such a device may comprise a local infusion catheter that delivers rapamycin at a rate controlled by the administrator.

Rapamycin may also be delivered systemically using an oral dosage form or a chronic injectible depot form or a patch to deliver rapamycin for a period ranging from about seven to forty-five days to achieve vascular tissue levels that are sufficient to inhibit negative remodeling. Such treatment is to be used to reduce or prevent restenosis when administered several days prior to elective angioplasty with or without a stent.

Data generated in porcine and rabbit models show that the release of rapamycin into the vascular wall from a nonerodible polymeric stent coating in a range of doses (35–430 ug/15–18 mm coronary stent) produces a peak fifty to fifty-five percent reduction in neointimal hyperplasia as set forth in Table 3 below. This reduction, which is maximal at about twenty-eight to thirty days, is typically not sustained in the range of ninety to one hundred eighty days in the porcine model as set forth in Table 4 below.

TABLE 3.0

Animal Studies with Rapamycin-coated stents
Values are mean ± Standard Error of Mean

Study	Duration	Stent ¹	Rapamycin	Neointimal Area		% Change From	
				N	(mm ²)	Polyme	Metal
Porcine							
98009	14 days	Metal		8	2.04 ± 0.17		
		1X + rapamycin	153 µg	8	1.66 ± 0.17*	-42%	-19%
		1X + TC300 + rapamycin	155 µg	8	1.51 ± 0.19*	-47%	-26%
99005	28 days	Metal		10	2.29 ± 0.21		
		1X + TC30 + rapamycin	130 µg	9	3.91 ± 0.60**		
		1X + TC100 + rapamycin	120 µg	8	2.81 ± 0.34		+23%
99006	28 days	Metal		9	2.62 ± 0.21		+14%
		EVA/BMA 3X		12	4.57 ± 0.46		
		1X + rapamycin	125 µg	12	5.02 ± 0.62		+10%
		3X + rapamycin	430 µg	11	2.84 ± 0.31* **	-43%	-38%
		3X + rapamycin	157 µg	12	3.06 ± 0.17* **	-39%	-33%
99011	28 days	Metal		12	2.77 ± 0.41* **	-45%	-39%
		1X + rapamycin	189 µg	11	3.09 ± 0.27		
		3X + rapamycin/dex	182/363 µg	11	4.52 ± 0.37		
		1X + rapamycin	181 µg	14	3.05 ± 0.35		-1%
		3X + rapamycin/dex	185/369 µg	14	2.72 ± 0.71		-12%
99021	60 days	Metal		12	2.14 ± 0.25		
		1X + rapamycin	181 µg	12	2.95 ± 0.38		+38%
99034	28 days	Metal		8	5.24 ± 0.58		
		1X + rapamycin	186 µg	8	2.47 ± 0.33**		-53%
		3X + rapamycin/dex	185/369 µg	6	2.42 ± 0.64**		-54%
20001	28 days	Metal		6	1.81 ± 0.09		
		1X + rapamycin	172 µg	5	1.66 ± 0.44		-8%
20007	30 days	Metal		9	2.94 ± 0.43		
		1XTC + rapamycin	155 µg	10	1.40 ± 0.11*		-52%*

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TABLE 3.0-continued

Animal Studies with Rapamycin-coated stents. Values are mean \pm Standard Error of Mean						
Study	Duration	Stent ¹	Rapamycin	Neointimal Area N (mm ²)	% Change From	
					Polyme	Metal
<u>Rabbit</u>						
99019	28 days	Metal		8 1.20 \pm 0.07		
		EVA/BMA 1X		10 1.26 \pm 0.16		+5%
		1X + rapamycin	64 μ g	9 0.92 \pm 0.14	-27%	-23%
		1X + rapamycin	196 μ g	10 0.66 \pm 0.12* **	-48%	-45%
99020	28 days	Metal		12 1.18 \pm 0.10		
		EVA/BMA 1X + rapamycin	197 μ g	8 0.81 \pm 0.16		-32%

¹Stent nomenclature: EVA/BMA 1X, 2X, and 3X signifies approx 500 μ g, 1000 μ g, and 1500 μ g total mass (polymer + drug), respectively.

TC, top coat of 30 μ g, 100 μ g, or 300 μ g drug-free BMA;

Biphasic; 2x 1X layers of rapamycin in EVA/BMA separated by a 100 μ g drug-free BMA layer.

²0.25 mg/kg/d \times 14 d preceded by a loading dose of 0.5 mg/kg/d \times 3d prior to stent implantation.

*p < 0.05 from EVA/BMA control.

**p < 0.05 from Metal;

³Inflammation score: (0 = essentially no intimal involvement;

1 = <25% intima involved;

2 = \geq 25% intima involved;

3 = >50% intima involved).

TABLE 4.0

180 day Porcine Study with Rapamycin-coated stents. Values are mean \pm Standard Error of Mean							
Study	Duration	Stent ¹	Rapamycin	N (mm ²)	% Change From		Inflammation Score #
					Polyme	Metal	
20007 (ETP-2-002233-P)	3 days	Metal		10 0.38 \pm 0.06			1.05 \pm 0.06
		1XTC + rapamycin	155 μ g	10 0.29 \pm 0.03	-24%		1.08 \pm 0.04
	30 days	Metal		9 2.94 \pm 0.43			0.11 \pm 0.08
		1XTC + rapamycin	155 μ g	10 1.40 \pm 0.11*	-52%*		0.25 \pm 0.10
	90 days	Metal		10 3.45 \pm 0.34			0.20 \pm 0.08
		1XTC + rapamycin	155 μ g	10 3.03 \pm 0.29	-12%		0.80 \pm 0.23
	180 days	1X + rapamycin	171 μ g	10 2.86 \pm 0.35	-17%		0.60 \pm 0.23
		Metal		10 3.65 \pm 0.39			0.65 \pm 0.21
	180 days	1XTC + rapamycin	155 μ g	10 3.34 \pm 0.31	-8%		1.50 \pm 0.34
		1X + rapamycin	171 μ g	10 3.87 \pm 0.28	+6%		1.68 \pm 0.37

The release of rapamycin into the vascular wall of a human from a nonerodible polymeric stent coating provides superior results with respect to the magnitude and duration of the reduction in neointimal hyperplasia within the stent as compared to the vascular walls of animals as set forth above.

Humans implanted with a rapamycin coated stent comprising rapamycin in the same dose range as studied in animal models using the same polymeric matrix, as described above, reveal a much more profound reduction in neointimal hyperplasia than observed in animal models, based on the magnitude and duration of reduction in neointima. The human clinical response to rapamycin reveals essentially total abolition of neointimal hyperplasia inside the stent using both angiographic and intravascular ultrasound measurements. These results are sustained for at least one year as set forth in Table 5 below.

TABLE 5.0

Patients Treated (N = 45 patients) with a Rapamycin-coated Stent			
Effectiveness Measures	Sirolimus FIM (N = 45 Patients, 45 Lesions)	95% Confidence Limit	
Procedure Success (QCA)	100.0% (45/45)	[92.1%, 100.0%]	
4-month In-Stent Diameter Stenosis (%)			
Mean \pm SD (N)	4.8% \pm 6.1% (30)	[2.6%, 7.0%]	
Range (min, max)	(-8.2%, 14.9%)		
6-month In-Stent Diameter Stenosis (%)			
Mean \pm SD (N)	8.9% \pm 7.6% (13)	[4.8%, 13.0%]	
Range (min, max)	(-2.9%, 20.4%)		
12-month In-Stent			

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TABLE 5.0-continued

Patients Treated (N = 45 patients) with a Rapamycin-coated Stent			
Effectiveness Measures	Sirolimus FIM (N = 45 Patients, 45 Lesions)	95% Confidence Limit	
<u>Diameter Stenosis (%)</u>			
Mean \pm SD (N)	8.9% \pm 6.1% (15)	[5.8%, 12.0%]	
Range (min, max)	(-3.0%, 22.0%)		
<u>4-month In-Stent Late Loss (mm)</u>			
Mean \pm SD (N)	0.00 \pm 0.29 (30)	[-0.10, 0.10]	
Range (min, max)	(-0.51, 0.45)		
<u>6-month In-Stent Late Loss (mm)</u>			
Mean \pm SD (N)	0.25 \pm 0.27 (13)	[0.10, 0.39]	
Range (min, max)	(-0.51, 0.91)		
<u>12-month In-Stent Late Loss (mm)</u>			
Mean \pm SD (N)	0.11 \pm 0.36 (15)	[-0.08, 0.29]	
Range (min, max)	(-0.51, 0.82)		
<u>4-month Obstruction Volume (%) (IVUS)</u>			
Mean \pm SD (N)	10.48% \pm 2.78% (28)	[9.45%, 11.51%]	
Range (min, max)	(4.60%, 16.35%)		
<u>6-month Obstruction Volume (%) (IVUS)</u>			
Mean \pm SD (N)	7.22% \pm 4.60% (13)	[4.72%, 9.72%]	
Range (min, max)	(3.82%, 19.88%)		
<u>12-month Obstruction Volume (%) (IVUS)</u>			
Mean \pm SD (N)	2.11% \pm 5.28% (15)	[0.00%, 4.78%]	
Range (min, max)	(0.00%, 19.89%)		
<u>6-month Target Lesion Revascularization (TLR)</u>			
0.0% (0/30)		[0.0%, 9.5%]	
<u>12-month Target Lesion Revascularization (TLR)</u>			
0.0% (0/15)		[0.0%, 18.1%]	

QCA = Quantitative Coronary Angiography

SD = Standard Deviation

IVUS = Intravascular Ultrasound

Rapamycin produces an unexpected benefit in humans when delivered from a stent by causing a profound reduction in in-stent neointimal hyperplasia that is sustained for at least one year. The magnitude and duration of this benefit in humans is not predicted from animal model data. Rapamycin used in this context includes rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

These results may be due to a number of factors. For example, the greater effectiveness of rapamycin in humans is due to greater sensitivity of its mechanism(s) of action toward the pathophysiology of human vascular lesions compared to the pathophysiology of animal models of angioplasty. In addition, the combination of the dose applied to the stent and the polymer coating that controls the release of the drug is important in the effectiveness of the drug.

As stated above, rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during angioplasty injury. Also, it is known that rapamycin prevents T-cell proliferation and differentiation when administered systemically. It has also been determined that rapamycin exerts a local inflammatory effect in the vessel wall when administered from a stent in low doses for a sustained period of time

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(approximately two to six weeks). The local anti-inflammatory benefit is profound and unexpected. In combination with the smooth muscle anti-proliferative effect, this dual mode of action of rapamycin may be responsible for its exceptional efficacy.

Accordingly, rapamycin delivered from a local device platform, reduces neointimal hyperplasia by a combination of anti-inflammatory and smooth muscle anti-proliferative effects. Rapamycin used in this context means rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin. Local device platforms include stent coatings, stent sheaths, grafts and local drug infusion catheters or porous balloons or any other suitable means for the in situ or local delivery of drugs, agents or compounds.

The anti-inflammatory effect of rapamycin is evident in data from an experiment, illustrated in Table 6, in which rapamycin delivered from a stent was compared with dexamethasone delivered from a stent. Dexamethasone, a potent steroidal anti-inflammatory agent, was used as a reference standard. Although dexamethasone is able to reduce inflammation scores, rapamycin is far more effective than dexamethasone in reducing inflammation scores. In addition, rapamycin significantly reduces neointimal hyperplasia, unlike dexamethasone.

TABLE 6.0

Group	N=	Neointimal Area (mm ²)	% Area Stenosis	Inflammation Score
Rapamycin				
Uncoated	8	5.24 \pm 1.65	54 \pm 19	0.97 \pm 1.00
Dexamethasone	8	4.31 \pm 3.02	45 \pm 31	0.39 \pm 0.24
(Dex)				
Rapamycin	7	2.47 \pm 0.94*	26 \pm 10*	0.13 \pm 0.19*
Rap + Dex	6	2.42 \pm 1.58*	26 \pm 18*	0.17 \pm 0.30*

*significance level P < 0.05

Rapamycin has also been found to reduce cytokine levels in vascular tissue when delivered from a stent. The data in FIG. 1 illustrates that rapamycin is highly effective in reducing monocyte chemotactic protein (MCP-1) levels in the vascular wall. MCP-1 is an example of a proinflammatory/chemotactic cytokine that is elaborated during vessel injury. Reduction in MCP-1 illustrates the beneficial effect of rapamycin in reducing the expression of proinflammatory mediators and contributing to the anti-inflammatory effect of rapamycin delivered locally from a stent. It is recognized that vascular inflammation in response to injury is a major contributor to the development of neointimal hyperplasia.

Since rapamycin may be shown to inhibit local inflammatory events in the vessel it is believed that this could explain the unexpected superiority of rapamycin in inhibiting neointima.

As set forth above, rapamycin functions on a number of levels to produce such desired effects as the prevention of T-cell proliferation, the inhibition of negative remodeling, the reduction of inflammation, and the prevention of smooth muscle cell proliferation. While the exact mechanisms of these functions are not completely known, the mechanisms that have been identified may be expanded upon.

Studies with rapamycin suggest that the prevention of smooth muscle cell proliferation by blockade of the cell cycle is a valid strategy for reducing neointimal hyperplasia. Dramatic and sustained reductions in late lumen loss and neointimal plaque volume have been observed in patients

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receiving rapamycin delivered locally from a stent. The present invention expands upon the mechanism of rapamycin to include additional approaches to inhibit the cell cycle and reduce neointimal hyperplasia without producing toxicity.

The cell cycle is a tightly controlled biochemical cascade of events that regulate the process of cell replication. When cells are stimulated by appropriate growth factors, they move from G_0 (quiescence) to the G_1 phase of the cell cycle. Selective inhibition of the cell cycle in the G_1 phase, prior to DNA replication (S phase), may offer therapeutic advantages of cell preservation and viability while retaining anti-proliferative efficacy when compared to therapeutics that act later in the cell cycle i.e. at S, G_2 or M phase.

Accordingly, the prevention of intimal hyperplasia in blood vessels and other conduit vessels in the body may be achieved using cell cycle inhibitors that act selectively at the G_1 phase of the cell cycle. These inhibitors of the G_1 phase of the cell cycle may be small molecules, peptides, proteins, oligonucleotides or DNA sequences. More specifically, these drugs or agents include inhibitors of cyclin dependent kinases (cdk's) involved with the progression of the cell cycle through the G_1 phase, in particular cdk2 and cdk4.

Examples of drugs, agents or compounds that act selectively at the G_1 phase of the cell cycle include small molecules such as flavopiridol and its structural analogs that have been found to inhibit cell cycle in the late G_1 phase by antagonism of cyclin dependent kinases. Therapeutic agents that elevate an endogenous kinase inhibitory protein^{kip} called P27, sometimes referred to as P27^{kip1}, that selectively inhibits cyclin dependent kinases may be utilized. This includes small molecules, peptides and proteins that either block the degradation of P27 or enhance the cellular production of P27, including gene vectors that can transfect the gene to produce P27. Staurosporin and related small molecules that block the cell cycle by inhibiting protein kinases may be utilized. Protein kinase inhibitors, including the class of tyrphostins that selectively inhibit protein kinases to antagonize signal transduction in smooth muscle in response to a broad range of growth factors such as PDGF and FGF may also be utilized.

Any of the drugs, agents or compounds discussed above may be administered either systemically, for example, orally, intravenously, intramuscularly, subcutaneously, nasally or intradermally, or locally, for example, stent coating, stent covering or local delivery catheter. In addition, the drugs or agents discussed above may be formulated for fast-release or slow release with the objective of maintaining the drugs or agents in contact with target tissues for a period ranging from three days to eight weeks.

As set forth above, the complex of rapamycin and FKBP12 binds to and inhibits a phosphoinositide (PI)-3 kinase called the mammalian Target of Rapamycin or TOR. An antagonist of the catalytic activity of TOR, functioning as either an active site inhibitor or as an allosteric modulator, i.e. an indirect inhibitor that allosterically modulates, would mimic the actions of rapamycin but bypass the requirement for FKBP12. The potential advantages of a direct inhibitor of TOR include better tissue penetration and better physical/chemical stability. In addition, other potential advantages include greater selectivity and specificity of action due to the specificity of an antagonist for one of multiple isoforms of TOR that may exist in different tissues, and a potentially different spectrum of downstream effects leading to greater drug efficacy and/or safety.

The inhibitor may be a small organic molecule (approximate mw<1000), which is either a synthetic or

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naturally derived product. Wortmanin may be an agent which inhibits the function of this class of proteins. It may also be a peptide or an oligonucleotide sequence. The inhibitor may be administered either systemically (orally, intravenously, intramuscularly, subcutaneously, nasally, or intradermally) or locally (stent coating, stent covering, local drug delivery catheter). For example, the inhibitor may be released into the vascular wall of a human from a nonerodible polymeric stent coating. In addition, the inhibitor may be formulated for fast-release or slow release with the objective of maintaining the rapamycin or other drug, agent or compound in contact with target tissues for a period ranging from three days to eight weeks.

As stated previously, the implantation of a coronary stent in conjunction with balloon angioplasty is highly effective in treating acute vessel closure and may reduce the risk of restenosis. Intravascular ultrasound studies (Mintz et al., 1996) suggest that coronary stenting effectively prevents vessel constriction and that most of the late luminal loss after stent implantation is due to plaque growth, probably related to neointimal hyperplasia. The late luminal loss after coronary stenting is almost two times higher than that observed after conventional balloon angioplasty. Thus, inasmuch as stents prevent at least a portion of the restenosis process, the use of drugs, agents or compounds which prevent inflammation and proliferation, or prevent proliferation by multiple mechanisms, combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

The local delivery of drugs, agents or compounds from a stent has the following advantages; namely, the prevention of vessel recoil and remodeling through the scaffolding action of the stent and the drugs, agents or compounds and the prevention of multiple components of neointimal hyperplasia. This local administration of drugs, agents or compounds to stented coronary arteries may also have additional therapeutic benefit. For example, higher tissue concentrations would be achievable than that which would occur with systemic administration, reduced systemic toxicity, and single treatment and ease of administration. An additional benefit of drug therapy may be to reduce the dose of the therapeutic compounds, thereby limiting their toxicity, while still achieving a reduction in restenosis.

There are a multiplicity of different stents that may be utilized following percutaneous transluminal coronary angioplasty. Although any number of stents may be utilized in accordance with the present invention, for simplicity, one particular stent will be described in exemplary embodiments of the present invention. The skilled artisan will recognize that any number of stents may be utilized in connection with the present invention.

A stent is commonly used as a tubular structure left inside the lumen of a duct to relieve an obstruction. Commonly, stents are inserted into the lumen in a non-expanded form and are then expanded autonomously, or with the aid of a second device in situ. A typical method of expansion occurs through the use of a catheter-mounted angioplasty balloon which is inflated within the stenosed vessel or body passageway in order to shear and disrupt the obstructions associated with the wall components of the vessel and to obtain an enlarged lumen. As set forth below, self-expanding stents may also be utilized.

FIG. 2 illustrates an exemplary stent 100 which may be utilized in accordance with an exemplary embodiment of the present invention. The expandable cylindrical stent 100 comprises a fenestrated structure for placement in a blood vessel, duct or lumen to hold the vessel, duct or lumen open,

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more particularly for protecting a segment of artery from restenosis after angioplasty. The stent 100 may be expanded circumferentially and maintained in an expanded configuration, that is circumferentially or radially rigid. The stent 100 is axially flexible and when flexed at a band, the stent 100 avoids any externally-protruding component parts.

The stent 100 generally comprises first and second ends with an intermediate section therebetween. The stent 100 has a longitudinal axis and comprises a plurality of longitudinally disposed bands 102, wherein each band 102 defines a generally continuous wave along a line segment parallel to the longitudinal axis. A plurality of circumferentially arranged links 104 maintain the bands 102 in a substantially tubular structure. Essentially, each longitudinally disposed band 102 is connected at a plurality of periodic locations, by a short circumferentially arranged link 104 to an adjacent band 102. The wave associated with each of the bands 102 has approximately the same fundamental spatial frequency in the intermediate section, and the bands 102 are so disposed that the wave associated with them are generally aligned so as to be generally in phase with one another. As illustrated in the figure, each longitudinally arranged band 102 undulates through approximately two cycles before there is a link to an adjacent band.

The stent 100 may be fabricated utilizing any number of methods. For example, the stent 100 may be fabricated from a hollow or formed stainless steel tube that may be machined using lasers, electric discharge milling, chemical etching or other means. The stent 100 is inserted into the body and placed at the desired site in an unexpanded form. In one embodiment, expansion may be effected in a blood vessel by a balloon catheter, where the final diameter of the stent 100 is a function of the diameter of the balloon catheter used.

It should be appreciated that a stent 100 in accordance with the present invention may be embodied in a shape-memory material, including, for example, an appropriate alloy of nickel and titanium. In this embodiment, after the stent 100 has been formed it may be compressed so as to occupy a space sufficiently small as to permit its insertion in a blood vessel or other tissue by insertion means, wherein the insertion means include a suitable catheter, or flexible rod. On emerging from the catheter, the stent 100 may be configured to expand into the desired configuration where the expansion is automatic or triggered by a change in pressure, temperature or electrical stimulation.

FIG. 3 illustrates an exemplary embodiment of the present invention utilizing the stent 100 illustrated in FIG. 2. As illustrated, the stent 100 may be modified to comprise a reservoir 106. Each of the reservoirs may be opened or closed as desired. These reservoirs 106 may be specifically designed to hold the drug, agent, compound or combinations thereof to be delivered. Regardless of the design of the stent 100, it is preferable to have the drug, agent, compound or combinations thereof dosage applied with enough specificity and a sufficient concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the bands 102 is preferably sized to adequately apply the drug/drug combination dosage at the desired location and in the desired amount.

In an alternate exemplary embodiment, the entire inner and outer surface of the stent 100 may be coated with various drug and drug combinations in therapeutic dosage amounts. A detailed description of exemplary coating techniques is described below.

Rapamycin or any of the drugs, agents or compounds described above may be incorporated into or affixed to the

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stent in a number of ways and utilizing any number of biocompatible materials. In the exemplary embodiment, the rapamycin is directly incorporated into a polymeric matrix and sprayed onto the outer surface of the stent. The rapamycin elutes from the polymeric matrix over time and enters the surrounding tissue. The rapamycin preferably remains on the stent for at least three days up to approximately six months and more preferably between seven and thirty days.

Any number of non-erodible polymers may be utilized in conjunction with rapamycin. In the exemplary embodiment, the polymeric matrix comprises two layers. The base layer comprises a solution of ethylene-co-vinylacetate and polybutylmethacrylate. The rapamycin is incorporated into this layer. The outer layer comprises only polybutylmethacrylate and acts as a diffusion barrier to prevent the rapamycin from eluting too quickly and entering the surrounding tissues. The thickness of the outer layer or top coat determines the rate at which the rapamycin elutes from the matrix. Essentially, the rapamycin elutes from the matrix by diffusion through the polymer molecules. Polymers are permeable, thereby allowing solids, liquids and gases to escape therefrom. The total thickness of the polymeric matrix is in the range from about 1 micron to about 20 microns or greater.

The ethylene-co-vinylacetate, polybutylmethacrylate and rapamycin solution may be incorporated into or onto the stent in a number of ways. For example, the solution may be sprayed onto the stent or the stent may be dipped into the solution. In a preferred embodiment, the solution is sprayed onto the stent and then allowed to dry. In another exemplary embodiment, the solution may be electrically charged to one polarity and the stent electrically changed to the opposite polarity. In this manner, the solution and stent will be attracted to one another. In using this type of spraying process, waste may be reduced and more control over the thickness of the coat may be achieved.

Since rapamycin works by entering the surrounding tissue, it is preferably only affixed to the surface of the stent making contact with one tissue. Typically, only the outer surface of the stent makes contact with the tissue. Accordingly, in a preferred embodiment, only the outer surface of the stent is coated with rapamycin. For other drugs, agents or compounds, the entire stent may be coated.

It is important to note that different polymers may be utilized for different stents. For example, in the above-described embodiment, ethylene-co-vinylacetate and polybutylmethacrylate are utilized to form the polymeric matrix. This matrix works well with stainless steel stents. Other polymers may be utilized more effectively with stents formed from other materials, including materials that exhibit superelastic properties such as alloys of nickel and titanium.

Although shown and described is what is believed to be the most practical and preferred embodiments, it is apparent that departures from specific designs and methods described and shown will suggest themselves to those skilled in the art and may be used without departing from the spirit and scope of the invention. The present invention is not restricted to the particular constructions described and illustrated, but should be constructed to cohere with all modifications that may fall within the scope of the appended claims.

What is claimed is:

1. A method for the treatment of intimal hyperplasia in vessel walls comprising the controlled delivery, by release, for a sustained period of time in the range from about two to about six weeks, from an implantable intraluminal medical device, of an anti-inflammatory agent in therapeutic dosage amounts, the anti-inflammatory agent comprises

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analog and congeners that bind a high affinity cytosolic protein, FKBP 12 and possesses the same pharmacologic properties as rapamycin.

2. Method for the treatment of intimal hyperplasia in vessel walls according to claim 1, wherein the anti-inflammatory agent reduces inflammatory cytokine levels in vascular tissues.

3. The method for the treatment of intimal hyperplasia in vessel walls according to claim 1, wherein the anti-inflammatory agent reduces monocyte chemotactic protein levels in vascular tissues.

4. The method for treatment of intimal hyperplasia in vessel walls according to claim 1, wherein the anti-inflammatory agent comprises rapamycin.

5. A drug delivery device comprising:

an implantable intraluminal medical device; and

a therapeutic dosage of an agent releasably affixed to the implantable intraluminal medical device for the treatment of inflammation caused by injury, the agent being released for a sustained period of time in the range from about two to about six weeks, the anti-inflammatory agent comprises analogs and congeners that bind a high affinity cytosolic protein, FKBP 12 and possess the same pharmacologic properties as rapamycin

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6. The drug delivery device according to claim 5, wherein the agent reduces inflammatory cytokine levels in vascular tissue.

7. The drug delivery device according to claim 5, wherein the agent reduces monocyte chemotactic protein levels in vascular tissues.

8. The drug delivery device according to claim 5, wherein the agent comprises rapamycin

9. The drug delivery device according to claim 5, wherein the intraluminal medical device comprises a stent

10. The drug delivery device according to claim 9, wherein the agent is incorporated in a non-erodible polymeric matrix coating affixed to the stent.

11. A method for the treatment of inflammation in vessel walls comprising the controlled delivery, by release, for a sustained period of time in the range from about two to about six weeks, from an implantable intraluminal medical device of an anti-inflammatory agent in therapeutic dosage amounts, the anti-inflammatory agent comprises analogs and congeners that bind a high affinity cytosolic protein, FKBP 12 and possess the same pharmacologic properties as rapamycin.

* * * * *

Exhibit D



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(12) **United States Patent**
Falotico et al.

(10) **Patent No.:** **US 7,217,286 B2**
 (45) **Date of Patent:** ***May 15, 2007**

(54) **LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT**

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(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

(63) Continuation of application No. 10/951,385, filed on Sep. 28, 2004, which is a continuation of application No. 10/408,328, filed on Apr. 7, 2003, now Pat. No. 6,808,536, which is a continuation of application No. 09/874,117, filed on Jun. 4, 2001, now Pat. No. 6,585,764, which is a continuation of application No. 09/061,568, filed on Apr. 16, 1998, now Pat. No. 6,273,913.

(60) Provisional application No. 60/044,692, filed on Apr. 18, 1997.

(51) **Int. Cl.**
 A61F 2/06 (2006.01)

(52) **U.S. Cl.** 623/1.42

(58) **Field of Classification Search** 623/1.45-1.48;
 427/2.1-2.31
 See application file for complete search history.

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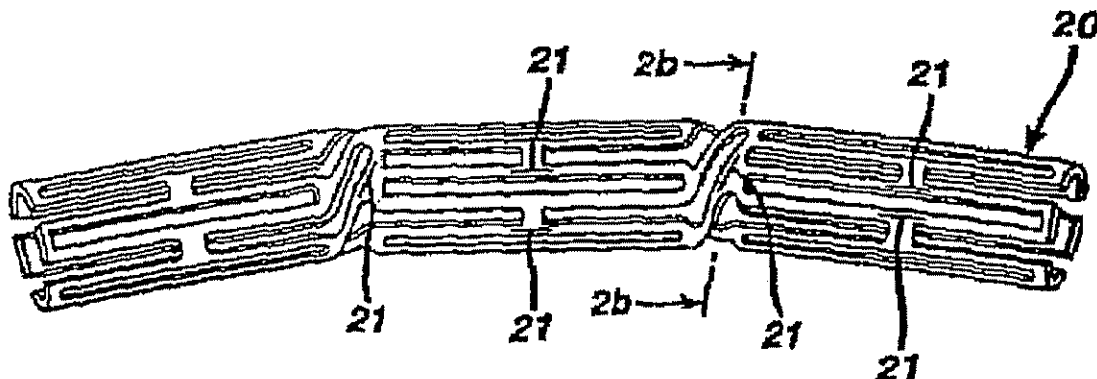
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(57) ABSTRACT

Methods of preparing intravascular stents with a polymeric coating containing macrocyclic lactone (such as rapamycin or its analogs), stents and stent graphs with such coatings, and methods of treating a coronary artery with such devices. The macrocyclic lactone-based polymeric coating facilitates the performance of such devices in inhibiting restenosis.

5 Claims, 2 Drawing Sheets



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FIG. 1

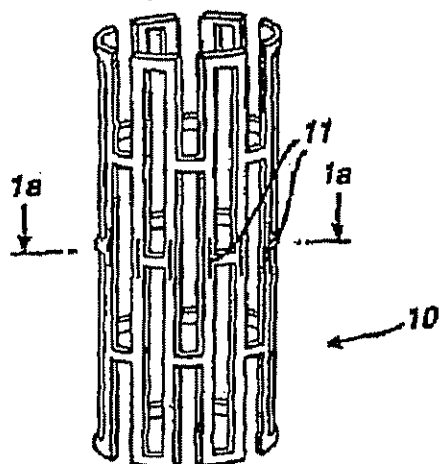


FIG. 1a

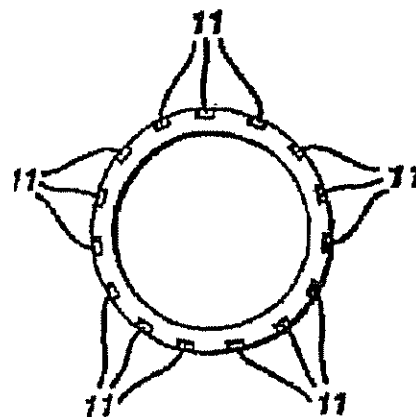


FIG. 2a

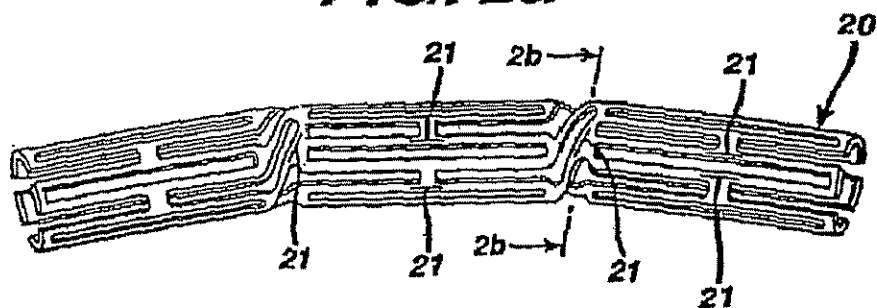
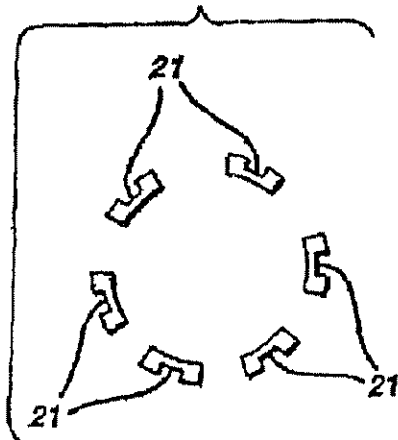


FIG. 2b



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FIG. 3a

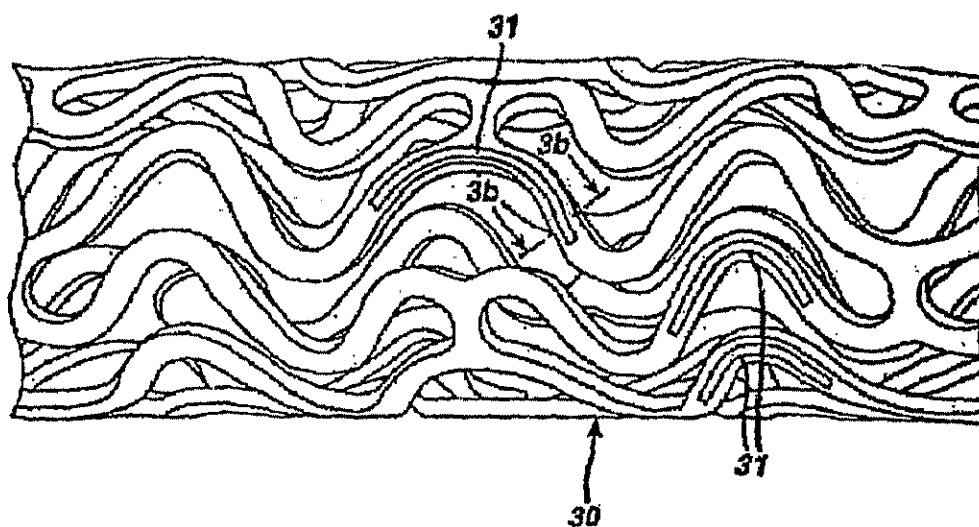
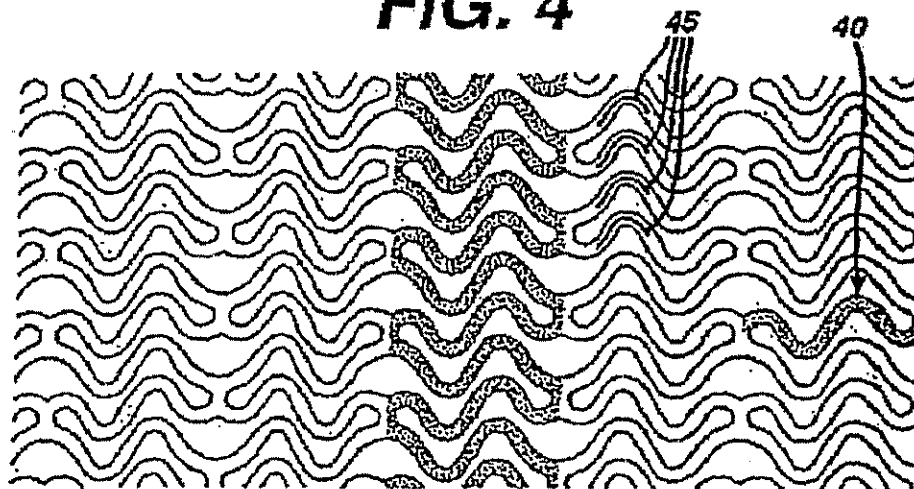


FIG. 3b



FIG. 4



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**LOCAL DELIVERY OF RAPAMYCIN FOR
TREATMENT OF PROLIFERATIVE
SEQUELAE ASSOCIATED WITH PTCA
PROCEDURES, INCLUDING DELIVERY
USING A MODIFIED STENT**

**CROSS-REFERENCE TO RELATED
APPLICATIONS**

This application is a continuation of Ser. No. 10/951,385, filed Sep. 28, 2004, now pending, which in turn is a continuation of Ser. No. 10/408,328, filed Apr. 7, 2003, now issued as U.S. Pat. No. 6,808,536, which in turn is a continuation of application Ser. No. 09/874,117, filed Jun. 4, 2001, now issued as U.S. Pat. No. 6,585,764, which is a continuation of application Ser. No. 09/061,568, filed Apr. 16, 1998, now issued as U.S. Pat. No. 6,273,913, which in turn claims benefit of provisional application Ser. No. 60/044,692, filed Apr. 18, 1997. The disclosures of these prior applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

BACKGROUND OF THE INVENTION

Re-narrowing (restenosis) of an arteriosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10–50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft. While the exact hormonal and cellular processes promoting restenosis are still being determined, our present understanding is that the process of PTCA, besides opening the arteriosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC). In response to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3–6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow.

Several recent experimental approaches to preventing SMC proliferation have shown promise although the mechanisms for most agents employed are still unclear. Heparin is the best known and characterized agent causing inhibition of SMC proliferation both in vitro and in animal models of balloon angioplasty-mediated injury. The mechanism of SMC inhibition with heparin is still not known but may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes c-fos and c-myc, 2) reduced cellular production of tissue plasminogen activator; are 3) binding and dequstration of growth regulatory factors such as fibrovalent growth factor (FGF).

Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon

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vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers, angiotensin converting enzyme inhibitors (captopril, cilazapril), cyclosporin A, trapidil (an antianginal, antiplatelet agent), terbinafine (antifungal), colchicine and taxol (antitubulin antiproliferatives), and c-myc and c-myb antisense oligonucleotides.

Additionally, a goat antibody to the SMC mitogen platelet derived growth factor (PDGF) has been shown to be effective in reducing myointimal thickening in a rat model of balloon angioplasty injury, thereby implicating PDGF directly in the etiology of restenosis. Thus, while no therapy has as yet proven successful clinically in preventing restenosis after angioplasty, the in vivo experimental success of several agents known to inhibit SMC growth suggests that these agents as a class have the capacity to prevent clinical restenosis and deserve careful evaluation in humans.

Coronary heart disease is the major cause of death in men over the age of 40 and in women over the age of fifty in the western world. Most coronary artery-related deaths are due to atherosclerosis. Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500,000–600,000 deaths in the United States annually. To arrest the disease process and prevent the more advanced disease states in which the cardiac muscle itself is compromised, direct intervention has been employed via percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG). PTCA is a procedure in which a small balloon-tipped catheter is passed down a narrowed coronary artery and then expanded to re-open the artery. It is currently performed in approximately 250,000–300,000 patients each year. The major advantage of this therapy is that patients in which the procedure is successful need not undergo the more invasive surgical procedure of coronary artery bypass graft. A major difficulty with PTCA is the problem of post-angioplasty closure of the vessel, both immediately after PTCA (acute reocclusion) and in the long term (restenosis).

The mechanism of acute reocclusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus. Recently, intravascular stents have been examined as a means of preventing acute reocclusion after PTCA.

Restenosis (chronic reocclusion) after angioplasty is a more gradual process than acute reocclusion: 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty. While the exact mechanism for restenosis is still under active investigation, the general aspects of the restenosis process have been identified.

In the normal arterial wall, smooth muscle cells (SMC) proliferate at a low rate (<0.1%/day; ref). SMC in vessel wall exists in a *contractile* phenotype characterized by 80–90% of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, golgi bodies, and free ribosomes are few and located in the perinuclear region. Extracellular matrix surrounds SMC and is rich in heparin-like glycosaminoglycans which are believed to be responsible for maintaining SMC in the contractile phenotypic state.

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the arterial wall become injured. Cell derived growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF),

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etc. released from platelets (i.e., PDGF) adhering to the damaged arterial luminal surface, invading macrophages and/or leukocytes, or directly from SMC (i.e., BFGF) provoke a proliferation and migratory response in medial SMC. These cells undergo a phenotypic change from the contractile phenotype to a synthetic phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum, golgi and free ribosomes. Proliferation/migration usually begins within 1-2 days post-injury and peaks at 2 days in the media, rapidly declining thereafter (Campbell et al., In: Vascular Smooth Muscle Cells in Culture, Campbell, J. H. and Campbell, G. R., Eds, CRC Press, Boca Ration, 1987, pp. 39-55); Clowes, A. W. and Schwartz, S. M., Circ. Res. 56:139-145, 1985).

Finally, daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate. Proliferation and migration continues until the damaged luminal endothelial layer regenerates at which time proliferation ceases within the intima, usually within 7-14 days postinjury. The remaining increase in intimal thickening which occurs over the next 3-6 months is due to an increase in extracellular matrix rather than cell number. Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response. (Liu et al., Circulation, 79:1374-1387, 1989).

Patients with symptomatic reocclusion require either repeat PTCA or CABG. Because 30-50% of patients undergoing PTCA will experience restenosis, restenosis has clearly limited the success of PTCA as a therapeutic approach to coronary artery disease. Because SMC proliferation and migration are intimately involved with the pathophysiological response to arterial injury, prevention of SMC proliferation and migration represents a target for pharmacological intervention in the prevention of restenosis.

SUMMARY OF THE INVENTION

Novel Features and Applications to Stent Technology
Currently, attempts to improve the clinical performance of stents have involved some variation of either applying a coating to the metal, attaching a covering or membrane, or embedding material on the surface via ion bombardment. A stent designed to include reservoirs is a new approach which offers several important advantages over existing technologies.

Local Drug Delivery from a Stent to Inhibit Restenosis

In this application, it is desired to deliver a therapeutic agent to the site of arterial injury. The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent. The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks, and be as thin as possible so as to minimize the increase in profile. In addition, the coating material should not contribute to any adverse response by the body (i.e., should be non-thrombogenic, non-inflammatory, etc.). To date, the ideal coating material has not been developed for this application.

An alternative would be to design the stent to contain reservoirs which could be loaded with the drug. A coating or membrane of biocompatible material could be applied over the reservoirs which would control the diffusion of the drug from the reservoirs to the artery wall.

One advantage of this system is that the properties of the coating can be optimized for achieving superior biocompat-

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ibility and adhesion properties, without the addition requirement of being able to load and release the drug. The size, shape, position, and number of reservoirs can be used to control the amount of drug, and therefore the dose delivered.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be better understood in connection with the following figures in which FIGS. 1 and 1A are top views and section views of a stent containing reservoirs as described in the present invention;

FIGS. 2a and 2b are similar views of an alternate embodiment of the stent with open ends;

FIGS. 3a and 3b are further alternate figures of a device containing a grooved reservoir; and

FIG. 4 is a layout view of a device containing a reservoir as in FIG. 3.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents. Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty. The calcium antagonists have also been unsuccessful in preventing restenosis, although they are still under study. Other agents currently under study include thromboxane inhibitors, prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al., 42 Ann. Rev. Med., 127-132 (1991); Popma et al., 84 Circulation, 1426-1436 (1991)).

Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements, thromboxane receptor antagonists, cholesterol lowering agents, and serotonin antagonists has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Franklin, S. M. and Faxon, D. P., 4 Coronary Artery Disease, 2-32-242 (1993); Serruys, P. W. et al., 88 Circulation, (part 1) 1588-1601, (1993)).

Conversely, stents have proven useful in preventing reducing the proliferation of restenosis. Stents, such as the stent 10 seen in layout in FIG. 4, balloon-expandable slotted metal tubes (usually but not limited to stainless steel), which when expanded within the lumen of an angioplastied coronary artery, provide structural support to the arterial wall. This support is helpful in maintaining an open path for blood flow. In two randomized clinical trials, stents were shown to increase angiographic success after PTCA, increase the stenosed blood vessel lumen and to reduce the lesion recurrence at 6 months (Serruys et al., 331 New Eng Jour. Med, 495, (1994); Fischman et al., 331 New Eng Jour. Med, 496-501 (1994). Additionally, in a preliminary trial, heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Additionally, heparin coating appears to have the added benefit of producing a reduction

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in sub-acute thrombosis after stent implantation (Serruys et al., 93 *Circulation*, 412-422, (1996). Thus, 1) sustained mechanical expansion of a stenosed coronary artery has been shown to provide some measure of restenosis prevention, and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs to local, injured tissue off the surface of the stent.

Numerous agents are being actively studied as antiproliferative agents for use in restenosis and have shown some activity in experimental animal models. These include: heparin and heparin fragments (Clowes and Karnovsky, 265 *Nature*, 25-626, (1977); Guyton, J. R. et al. 46 *Circ. Res.*, 625-634, (1980); Clowes, A. W. and Clowes, M. M., 52 *Lab. Invest.*, 611-616, (1985); Clowes, A. W. and Clowes, M. M., 58 *Circ. Res.*, 839-845 (1986); Majesky et al., 61 *Circ. Res.*, 296-300, (1987); Snow et al., 137 *Am. J. Pathol.*, 313-330 (1990); Okada, T. et al., 25 *Neurosurgery*, 92-898, (1989) colchicine (Currier, J. W. et al., 80 *Circulation*, 11-66, (1989), taxol (ref), angiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., 245 *Science*, 186-188 (1989), angiopeptin (Lundergan, C. F. et al., 17 *Am. J. Cardiol. (Suppl. B)*; 132B-136B (1991), Cyclosporin A (Jonasson, L. et al., 85 *Proc. Natl. Acad. Sci.*, 2303 (1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., 253 *Science*, 1129-1132 (1991), terbinafine (Nemecek, G. M. et al., 248 *J. Pharmacol. Exp. Thera.*, 1167-11747 (1989), rapamycin (Liu, M. W. et al., 81 *Circulation*, 1089-1093 (1990), interferon-gamma (Hansson, G. K. and Holm, 84 *J. Circulation*, 1266-1272 (1991), steroids (Colburn, M. D. et al., 15 *J. Vasc. Surg.*, 510-518 (1992), see also Berk, B. C. et al., 17 *J. Am. Coll. Cardiol.*, 111B-117B (1991), ionizing radiation (ref), fusion toxins (ref) antisense oligonucleotides (ref), gene vectors (ref), and rapamycin (see below).

Of particular interest in rapamycin. Rapamycin is a macrolide antibiotic which blocks IL-2-mediated T-cell proliferation and possesses antiinflammatory activity. While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G sub 1 to 5 phase progression of T-cells through the cell cycle by inhibiting specific cell cyclins and cyclin-dependent protein kinases (Siekierka, *Immunol. Res.* 13: 110-116, 1994). The antiproliferative action of rapamycin is not limited to T-cells; Marx et al. (*Circ Res* 76:412-417, 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC in vitro while Poon et al. have shown the rat, porcine, and human SMC migratin can also be inhibited by rapamycin (*J Clin Invest* 98: 2277-2283, 1996). Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response. In fact, the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in a rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al., *Transplantation* 55:1409-1418, 1993; Gallo et al., in press, (1997)). These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis.

Although the ideal agent for restenosis has not yet been identified, some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury, including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications. Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of

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SMC combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis

Experiments

Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression.

Delivery Methods: These can vary:

Local delivery of such agents (rapamycin) from the struts of a stent, from a stent graft, grafts, stent cover or sheath.

Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft.

or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein.

or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e.g. vapour deposition methods such as rf-plasma polymerization) and combinations thereof.

Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake.

Extravascular delivery by the pericardial route.

Extravascular delivery by the advential application of sustained release formulations.

Uses:

for inhibition of cell proliferation to prevent neointimal proliferation and restenosis.

prevention of tumor expansion from stents.

preventing growth of tissue into catheters and shunts inducing their failure.

1. Experimental Stent Delivery Method—Delivery from Polymer Matrix:

Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0.001 weight % to 30 weight % of drug. Polymers are biocompatible (i.e., not elicit any negative tissue reaction or promote mural thrombus formation) and degradable, such as lactone-based polyesters or copolyesters, e.g., polylactide, polycaprolactone-glycolide, polyorthoesters, polyanhydrides; poly-amino acids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, e.g., PEO-PLLA, or blends thereof. Nonabsorbable biocompatible polymers are also suitable candidates. Polymers such as polydimethylsiloxane; poly(ethylene-vinylacetate); acrylate based polymers or copolymers, e.g., poly(hydroxyethyl methacrylate), polyvinyl pyrrolidone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters.

Polymer/drug mixture is applied to the surfaces of the stent by either dip-coating, or spray coating, or brush coating or dip/spin coating or combinations thereof, and the solvent allowed to evaporate to leave a film with entrapped rapamycin.

2. Experimental Stent Delivery Method—Delivery from Microporous Depots in Stent Through a Polymer Membrane Coating:

Stent, whose body has been modified to contain micropores or channels is dipped into a solution of Rapamycin, range 0.001 wt % to saturated, in organic solvent such as acetone or methylene chloride, for sufficient time to allow solution to permeate into the pores. (The dipping solution can also be compressed to improve the loading efficiency.) After solvent has been allowed to evaporate, the stent is dipped briefly in fresh solvent to remove excess surface bound drug. A solution of polymer, chosen from any identified in the first experimental method, is applied to the

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stent as detailed above. This outer layer of polymer will act as diffusion-controller for release of drug.

3. Experimental Stent Delivery Method—Delivery Via Lysis of a Covalent Drug Tether:

Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization. Covalent bonds such as ester, amides or anhydrides may be suitable for this.

4. Experimental Method—Pericardial Delivery:

A: Polymeric Sheet

Rapamycin is combined at concentration range previously highlighted, with a degradable polymer such as poly(caprolactone-glycolid-e) or non-degradable polymer, e.g., polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10 μ m to 1000 μ m. The resulting sheet can be wrapped perivascularly on the target vessel. Preference would be for the absorbable polymer.

B: Conformal Coating:

Rapamycin is combined with a polymer that has a melting temperature just above 37° C., range 40°–45° C. Mixture is applied in a molten state to the external side of the target vessel. Upon cooling to body temperature the mixture solidifies conformably to the vessel wall. Both non-degradable and absorbable biocompatible polymers are suitable.

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin. As seen in FIGS. 1a, 2a and 3a, any stent strut 10, 20, 30 can be modified to have a certain reservoir or channel 11, 21, 31. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. FIG. 4 shows a stent 40 with a reservoir 45 created at the apex of a flexible strut. Of course, this reservoir 45 is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents.

In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and

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enough concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must be kept at a size of about 0.0005" to about 0.003". Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

These and other concepts will be disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be perceived to fall within the scope of the invention which is to be realized from the attached claims and their equivalents.

What is claimed:

1. A device comprising a metallic stent, a biocompatible, nonabsorbable polymeric carrier, and a therapeutic agent, wherein:

said polymeric carrier comprises an acrylate-based polymer or copolymer, a fluorinated polymer, or a mixture thereof, and

said therapeutic agent is rapamycin, or a macrocyclic lactone analog thereof, and is present in an amount effective to inhibit neointimal proliferation.

2. The device according to claim 1 wherein said therapeutic agent is a macrocyclic lactone analog of rapamycin.

3. The device according to claim 1 that provides a controlled release of said therapeutic agent over a period of several weeks.

4. The device according to claim 2 that provides a controlled release of said therapeutic agent over a period of several weeks.

5. A method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting a device according to any one of claims 1 to 4 in the lumen of said coronary artery.

* * * * *

Exhibit E



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/951,385	05/29/2007	7223286	JJI-51-CON2	7537

27777 7590 05/09/2007
 PHILIP S. JOHNSON
 JOHNSON & JOHNSON
 ONE JOHNSON & JOHNSON PLAZA
 NEW BRUNSWICK, NJ 08933-7003

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
 (application filed on or after May 29, 2000)

The Patent Term Adjustment is 265 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

Carol Wright, Somerset, NJ;
 Gerard H. Llanos, Stewartsville, NJ;
 Ronald Rakos, Neshanic Station, NJ;
 Kristin King, Mahwah, NJ;
 Robert Falotico, Bell Mead, NJ;

U.S. PATENT NO. 7,223,286

Exhibit F

January 20, 2006

Prudential Equity Group, LLCHealthcare
Medical Devices**JNJ: TAKES OFF THE GLOVES IN ITS FIGHT WITH BOSTON SCIENTIFIC FOR GUIDANT****Johnson & Johnson**Larry Blegelsen • 212.778.5825 • lawrence_blegelsen@prusec.com
Steve Beuchaw • 212.778.1515 • steve_beuchaw@prusec.comCurrent: Underweight
Risk: Low
Target: \$59.00
Industry: Favorable

All important disclosures and Regulation AC disclosure can be found at the end of this report, starting at page 6, under the section entitled Important Disclosures and Regulation AC Disclosure, respectively.

Includes Option Expenses

	FY	REV	EPS	P/E	1Q	2Q	3Q	4Q
Actual	12/04	\$47,348.0E	\$2.99E	20.6X	\$0.80A	\$0.79A	\$0.75A	\$0.64A
Current	12/05	\$51,214.0E	\$3.37E	18.2X	\$0.94A	\$0.90A	\$0.85A	\$0.69E
Current	12/06	\$53,758.0E	\$3.61E	17.0X	\$1.01E	\$0.95E	\$0.89E	\$0.76E

Without Option Expenses

	FY	REV	EPS	P/E	1Q	2Q	3Q	4Q
Actual	12/04	\$47,348.0E	\$3.10A	19.8X	\$0.83A	\$0.82A	\$0.78A	\$0.67A
Current	12/05	\$51,214.0E	\$3.49E	17.6X	\$0.87A	\$0.93A	\$0.87A	\$0.72E
Current	12/06	\$53,758.0E	\$3.74E	16.4X	\$1.04E	\$0.98E	\$0.93E	\$0.79E

Avg. Volume: 8,700,000
Market Cap: \$181,808 m
Shares: 3,119.84 mDiv/Yield: 1.32/2.15%
52w Range: 70.00-59.80EPS Growth: NA
P/E / Growth: NM**HIGHLIGHTS**

- As the 1/25 deadline to make a counter-offer for GDT approaches, JNJ is communicating to the Street that BSX's \$80/share offer for GDT is fraught with uncertainty which leads us to believe that JNJ is still very interested in acquiring GDT and that JNJ will likely increase its offer at least one more time.
- We believe JNJ will have to raise its offer to about \$78/share from \$71/share in order to gain the GDT board's approval.
- Although a JNJ offer of \$78/share would be 3% below BSX's, there is precedent for a board to accept a lower offer. In 5/05, Verizon acquired MCI for \$8.44B or 13% less than what Qwest offered because Verizon was seen as a more stable company.
- JNJ claims that 2 of its patents may be infringed if a company tries to launch a drug-eluting stent coated with a rapamycin derivative such as ABT's zotarolimus and GDT's everolimus. The potential for JNJ to prevent ABT and BSX from marketing the Xience-V DES, could give the GDT board pause for approving a BSX-GDT merger.
- Our analysis indicates that an offer of \$78/share for GDT would be slightly more dilutive for JNJ compared to its current \$71/share offer but still accretive on a cash basis in '08. In addition, our analysis indicates that JNJ could offer \$90/share for GDT before an acquisition of STJ is more attractive.

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DISCUSSION

As the January 25th deadline for JNJ to make a counter-offer for Guidant (GDT-\$75.89; Neutral Weight Rated) approaches, JNJ is communicating to the Street that Boston Scientific's (BSX-\$23.36; Neutral Weight Rated) \$80/share offer for GDT is fraught with uncertainty. This leads us to believe that JNJ is still very much interested in acquiring GDT and that JNJ will likely increase its offer for GDT at least one more time. We believe JNJ will have to increase its offer to at least \$78/share from its previous offer of \$71/share if it hopes to gain the GDT board's approval. Although a JNJ offer of \$78/share would be 3% below BSX's, there is precedent for a board and shareholders to accept a lower offer. In May 2005, Verizon acquired MCI for \$8.44 billion or 13% less than what Qwest offered because VZ was seen as a more stable company. During the bidding process, Q forced VZ to raise its offer for MCI from \$20.35/share to \$26/share. Although the situation with VZ and Q is not a perfect analogy, we could envision a similar scenario playing out with GDT given the lower risk associated with the JNJ offer and the greater liquidity of JNJ shares compared to BSX shares once a deal is completed. Interestingly, BSX's stock price is moving closer to the lower end of the collar (\$22.62). If BSX's stock price falls to \$22.00, its offer for GDT would become \$79/share (see Figure 1 below).

Figure 1: Impact of Collar on BSX's Offer For GDT if BSX's Share Price Reaches \$22.00

BSX Current Price:	\$23.36
Collar Max:	\$28.86
Collar Min:	\$22.62
Proposed Cash Component of BSX Offer:	\$42.00
Proposed Stock Component of BSX Offer:	\$38.00
Proposed Total BSX Offer for GDT:	\$80.00
Assumed BSX Stock Price:	\$22.00
Collared Exchange Ratio:	1.68
Resulting Stock Component of BSX Offer:	\$36.96
Resulting Total Value of BSX Offer:	\$78.96
Lost Value Per GDT Share:	-\$1.04
GDT Fully Diluted Shares (mm):	335
Market Value Impact (\$mm):	-\$349
Source: Company reports, Prudential Equity Group, LLC estimates, Reuters.	

JNJ's acquisition of GDT has already received regulatory clearance in the U.S. and E.U. In order to receive approval from the FTC, JNJ was forced to license out rapid exchange (RX) stent technology as well as certain JNJ patents which cover the use of rapamycin derivatives such as Novartis's (NVS: \$54.98; Overweight rated by Prudential Equity Group's Senior Pharmaceutical Analyst, Tim Anderson) everolimus and Abbott Labs' (ABT-\$40.60; Neutral Weight Rated) zotarolimus on a stent because the FTC wanted to ensure that ABT would be a viable competitor in the drug-eluting stent (DES) market. ABT is currently developing a DES using its proprietary drug, zotarolimus which is also used on Medtronic's (MDT-\$58.99; Overweight Rated) Endeavor DES. The clinical results for Endeavor have

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been mixed thus far and data with ABT's DES, ZoMaxx, have not been presented yet so it's unclear how competitive ZoMaxx will be. Under the JNJ-GDT deal, ABT would be able to potentially develop a second DES using everolimus. Although ABT does not currently have the rights to use the drug everolimus on a stent from NVS, the drug's originator, it is our understanding that acquiring the rights would not be a major obstacle if ABT wanted to develop an everolimus-coated stent.

If BSX acquires GDT, BSX would sell GDT's vascular intervention (VI) business, including shared rights to GDT's promising everolimus-coated stent, Xience-V, to ABT. Although JNJ's patents have never been litigated, JNJ believes it has a strong intellectual property (IP) position with regard to the use of rapamycin derivatives on a stent. JNJ could pursue a preliminary injunction if ABT and BSX try to launch an everolimus-coated or zotarolimus-coated stent. The potential for JNJ to prevent ABT and BSX from marketing the Xience-V DES, could give the GDT board and the FTC pause for approving a BSX-GDT merger. According to JNJ, the key patents are the Falotico (6,776,796) and Wright (6,585,764) patents.

Our analysis indicates that an offer of \$78/share for GDT would be slightly more dilutive for JNJ on a cash and GAAP basis compared to its current \$71/share offer but still accretive on a cash basis in 2008 (see merger models at the end of this note). In our model, we assume that JNJ raises the cash portion of its offer by \$6/share. In addition, our analysis indicates that JNJ could offer \$90/share for GDT before an acquisition of St. Jude is more attractive financially for JNJ (also shown at the end of this note).

VALUATION AND RISKS

Our price target of \$59 is the average of our price targets for J&J with and without GDT. For JNJ alone, we apply a target multiple of 13.0x our 2008 EPS of \$4.38 to arrive at a target price of \$57. We use a multiple of 13x, a 7% discount to the average multiple of the large cap U.S. pharmaceutical group, which is appropriate in our view because of JNJ's slowing pharmaceutical growth (the source of 50% of JNJ's profits). We use 2008 EPS because that is the first year in which the GDT acquisition is expected to be accretive. For JNJ with GDT, we apply a target multiple of 14x our combined JNJ-GDT EPS estimate of \$4.40 to arrive at a target price of \$62. We use a multiple of 14x because this represents a 15% discount to our coverage universe which we believe is appropriate given the combined entity's below average growth prospects. Again, we use 2008 EPS because that is the first year in which the GDT acquisition would be accretive.

The average of the two scenarios yields a target price of \$59.

Key risks to the achievement of our price target are: 1) less price erosion in the U.S. EPO market than we model; 2) branded and generic competition in the European EPO market takes less share of the market than we model; 3) Cypher captures greater market share from Taxus than what we model; 4) key pharmaceutical pipeline products such as paliperidone ER exceed our expectations; 5) JNJ acquires GDT; 6) JNJ's operating expenses grow more slowly than what we model; and 7) JNJ acquires additional late stage pharmaceutical products.

BUSINESS

Johnson & Johnson (JNJ), is the world's most comprehensive and broadly based manufacturer of health care products, as well as a provider of related services, for the consumer, pharmaceutical, and medical devices and diagnostics markets.

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CHARTS/MODELS**Guidant Impact on JNJ Cash EPS, GAAP EPS and Growth - \$71 per Share (57% cash/43% stock)***In Millions, Except Per Share Data*

Revenue Impact of GDT (\$MM)	2005 E	2006 E	2007 E	2008 E	2009 E	2010 E	CAGR		
							'05-'08	'05-'10	'07-'10
JNJ Sales (ex-GDT)	\$61,186	\$63,818	\$67,263	\$80,888	\$63,778	\$88,781	6.0%	6.1%	6.3%
Total Incremental Sales (Guidant)	\$3,649	\$3,889	\$4,478	\$5,236	\$6,842	\$8,600	13.8%	12.8%	13.2%
Total JNJ-GDT Pro Forma Sales	\$64,735	\$67,718	\$71,742	\$86,231	\$69,720	\$97,280	8.8%	8.8%	8.8%
Pro-Forma Y-Y %		5.5%	7.0%	7.3%	5.3%	8.0%			
JNJ Growth Ex-GDT	8.1%	5.1%	6.4%	6.5%	4.6%	7.9%			
Sales Growth Impact of GDT		0.3%	0.6%	0.8%	0.7%	0.1%			
Profit Impact									
Total Incremental Operating Profit		832	1,264	1,581	1,880	2,132			
Merger Synergies		0	0	0	0	0			
GDT Other Expenses		12	23	41	63	63			
Profit w/Synergies and GDT Other Expenses		820	1,231	1,551	1,807	2,078			
After Tax GDT Income		623	838	1,178	1,373	1,580			
Impact on JNJ Interest Income - After Tax		-378	358	-328	293	-248			
Net Impact on JNJ Net Profit		245	577	850	1,681	1,331			
	2005 E	2006 E	2007 E	2008 E	2009 E	2010 E	CAGR		
							'05-'08	'05-'10	'07-'10
Pro GDT JNJ EPS	3.49	3.74	4.08	4.38	4.52	4.98	7.8%	7.4%	8.8%
JNJ Cash EPS with GDT		3.82	4.08	4.42	4.83	5.15	8.2%	8.1%	8.2%
GDT Impact on Cash EPS		-0.11	-0.02	0.05	0.11	0.17			
Amort of Intang. Per Share (Non-Cash)		(0.18)	(0.16)	(0.16)	(0.16)	(0.18)			
JNJ GAAP EPS with GDT		\$3.48	\$3.80	\$4.28	\$4.47	\$4.89			
GDT Impact on JNJ GAAP EPS		(0.27)	(0.18)	(0.12)	(0.05)	0.00			
Growth Impact of GDT									
Pro GDT JNJ EPS Y-Y		7.1%	9.4%	7.1%	3.3%	10.2%			
JNJ EPS ex Amort of GDT Intangibles		3.6%	12.1%	8.8%	4.7%	11.1%			
Impact of GDT ex Amort. of Intangibles		-3.2%	2.7%	1.8%	1.4%	1.0%			
JNJ GAAP EPS Y-Y with GDT Intangibles		-0.8%	12.6%	8.3%	4.8%	11.5%			
GDT Impact on GAAP EPS Growth		-7.8%	3.3%	2.2%	1.6%	1.4%			

*A Actuals**E Prudential Equity Group Estimates*

Source: Prudential Equity Group, LLC, and Company Reports

Assumes JNJ shares are worth \$62.00

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Guidant Impact on JNJ Cash EPS, GAAP EPS and Growth - \$78 per Share (61% cash/39% stock)

In Millions, Except Per Share Data

Revenue Impact of GDT (\$MM)	2005 E	2006 E	2007 E	2008 E	2009 E	2010 E	CAGR		
							'05-'08	'08-'10	'07-'10
JNJ Sales (ex-GDT)	\$51,185	\$53,819	\$57,283	\$60,999	\$63,778	\$68,781	8.0%	8.1%	8.3%
Total Incremental Sales (Guidant)	\$3,549	\$3,899	\$4,478	\$5,235	\$5,942	\$8,500	13.8%	12.9%	13.2%
Total JNJ GDT Pro Forma Sales	\$54,735	\$57,718	\$61,762	\$66,234	\$69,720	\$77,281	8.8%	8.6%	8.8%
Pro-Forma Y-Y %		5.5%	7.0%	7.3%	5.3%	8.0%			
JNJ Growth Ex-GDT	8.1%	5.1%	6.4%	6.5%	4.6%	7.9%			
Sales Growth Impact of GDT		0.3%	0.6%	0.8%	0.7%	0.1%			
Profit Impact									
Total Incremental Operating Profit		632	1,254	1,591	1,880	2,132			
Merger Synergies		0	0	0	0	0			
GDT Other Expenses		12	23	41	53	53			
Profit w/Synergies and GDT Other Expenses		620	1,231	1,551	1,827	2,079			
After Tax GDT Income		623	938	1,178	1,373	1,580			
Impact on JNJ Interest Income - After Tax		-458	-439	-409	-373	-329			
Net Impact on JNJ Net Profit		165	497	769	1,000	1,251			
	2005 E	2006 E	2007 E	2008 E	2009 E	2010 E	CAGR		
							'05-'08	'08-'10	'07-'10
Pro GDT JNJ EPS	3.48	3.74	4.09	4.38	4.52	4.88	7.9%	7.4%	8.8%
JNJ Cash EPS with GDT		3.80	4.04	4.40	4.81	5.12	8.0%	8.0%	8.3%
GDT Impact on Cash EPS		-0.14	-0.05	0.02	0.09	0.14			
Amort of Intang. Per Share (Non-Cash)		(0.10)	(0.16)	(0.18)	(0.18)	(0.18)			
JNJ GAAP EPS with GDT		\$3.44	\$3.87	\$4.23	\$4.44	\$4.98			
GDT Impact on JNJ GAAP EPS		(0.30)	(0.21)	(0.14)	(0.08)	(0.02)			
Growth Impact of GDT									
Pro GDT JNJ EPS Y-Y		7.1%	9.4%	7.1%	3.3%	10.2%			
JNJ EPS ex-Amort of GDT Intangibles		3.2%	12.2%	9.0%	4.8%	11.2%			
Impact of GDT ex-Amort. of Intangibles		-3.8%	2.8%	1.8%	1.5%	1.0%			
JNJ GAAP EPS Y-Y with GDT Intangibles		-1.5%	12.7%	9.3%	4.0%	11.8%			
GDT Impact on GAAP EPS Growth		-8.8%	3.3%	2.2%	1.7%	1.4%			

A Actuals**E Prudential Equity Group Estimates**

Source: Prudential Equity Group, LLC, and Company Reports

Assumes JNJ shares are worth \$82.00

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To view charts associated with those stocks mentioned in this report, please visit <http://cm1.prusec.com>.

REGULATION AC DISCLOSURE

Larry Biegelsen is principally responsible for the analysis of any security or issuer included in this report and certifies that the views expressed accurately reflect such research analyst's personal views about subject securities or issuers and certifies that no part of his or her compensation was, is, or will be directly or indirectly related to the specific recommendation or views contained in the research report.

IMPORTANT DISCLOSURES

Prudential Financial or its affiliates beneficially owns 1% or more of any class of common equity securities of St. Jude Medical.

When we assign an **Overweight** rating, we mean that we expect that the stock's total return will exceed the average total return of all of the stocks covered by the analyst (or analyst team). Our investment time frame is 12-18 months except as otherwise specified by the analyst in the report.

When we assign a **Neutral Weight** rating, we mean that we expect that the stock's total return will be in line with the average total return of all of the stocks covered by the analyst (or analyst team). Our investment time frame is 12-18 months except as otherwise specified by the analyst in the report.

When we assign an **Underweight** rating, we mean that we expect that the stock's total return will be below the average total return of all of the stocks covered by the analyst (or analyst team). Our investment time frame is 12-18 months except as otherwise specified by the analyst in the report.

ANALYST UNIVERSE COVERAGE:

Larry Biegelsen: Abbott Laboratories, Boston Scientific, Edwards Lifesciences, Johnson & Johnson, St. Jude Medical, Medtronic, Inc., Guidant Corp.

Tim Anderson, M.D.: Schering-Plough, Eli Lilly, Forest Laboratories, Merck & Co., Bristol-Myers Squibb, Wyeth, Pfizer, Inc., GlaxoSmithKline plc, AstraZeneca, Novartis AG, Roche Holding AG, Sanofi-Aventis Group.

Rating Distribution

01/19/06	Firm	Firm's Investment Banking Clients	Sector	Sector's Investment Banking Clients
Overweight(Buy)*	30%	0%	29%	0%
Neutral Weight(Hold)*	48%	0%	53%	0%
Underweight(Sell)*	22%	0%	17%	0%

Excludes Closed End Funds

12/30/05	Firm	Firm's Investment Banking Clients	Sector	Sector's Investment Banking Clients
Overweight(Buy)*	30%	0%	31%	0%
Neutral Weight(Hold)*	47%	0%	52%	0%
Underweight(Sell)*	23%	0%	17%	0%

Excludes Closed End Funds

09/30/05	Firm's	Sector's
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	Firm	Investment Banking Clients	Sector	Investment Banking Clients
Overweight(Buy)*	32%	0%	29%	0%
Neutral Weight(Hold)*	44%	0%	49%	0%
Underweight(Sell)*	24%	0%	22%	0%

Excludes Closed End Funds

06/30/05	Firm	Firm's Investment Banking Clients	Sector	Sector's Investment Banking Clients
Overweight(Buy)*	32%	0%	31%	0%
Neutral Weight(Hold)*	45%	0%	51%	0%
Underweight(Sell)*	22%	0%	19%	0%

Excludes Closed End Funds

* In accordance with applicable rules and regulations, we note above parenthetically that our stock ratings of "Overweight," "Neutral Weight," and "Underweight" most closely correspond with the more traditional ratings of "Buy," "Hold," and "Sell," respectively; however, please note that their meanings are not the same. (See the definitions above.) We believe that an investor's decision to buy or sell a security should always take into account, among other things, that the investor's particular investment objectives and experience, risk tolerance, and financial circumstances. Rather than being based on an expected deviation from a given benchmark (as buy, hold and sell recommendations often are), our stock ratings are determined on a relative basis (see the foregoing definitions).

Prior to September 8, 2003 our rating definitions were Buy, Hold, Sell. They are defined as follows:

When we assign a **Buy** rating, we mean that we believe that a stock of average or below-average risk offers the potential for total return of 15% or more over the next 12 to 18 months. For higher-risk stocks, we may require a higher potential return to assign a Buy rating. When we reiterate a Buy rating, we are stating our belief that our price target is achievable over the next 12 to 18 months.

When we assign a **Sell** rating, we mean that we believe that a stock of average or above-average risk has the potential to decline 15% or more over the next 12 to 18 months. For lower-risk stocks, a lower potential decline may be sufficient to warrant a Sell rating. When we reiterate a Sell rating, we are stating our belief that our price target is achievable over the next 12 to 18 months.

A **Hold** rating signifies our belief that a stock does not present sufficient upside or downside potential to warrant a Buy or Sell rating, either because we view the stock as fairly valued or because we believe that there is too much uncertainty with regard to key variables for us to rate the stock a Buy or Sell.

When we assign an industry rating of **Favorable**, we mean that generally industry fundamentals/stock prospects are improving.

When we assign an industry rating of **Neutral**, we mean that generally industry fundamentals/stock prospects are stable.

When we assign an industry rating of **Unfavorable**, we mean that generally industry fundamentals/stock prospects are deteriorating.

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Ratings History: JNJ

Rating Changes				Target Price Changes			
Date	From	To	Analyst	Date	From	To	Analyst
12/08/05	---	UNDR	Biegelsen	12/08/05	---	59.00	Biegelsen
03/31/05	OVER	---	Faulkner	03/31/05	74.00	---	Faulkner
08/20/04	---	OVER	Faulkner	12/16/04	61.00	74.00	Faulkner
				08/20/04	---	61.00	Faulkner

Additional Information**Price Target – Methods/Risks**

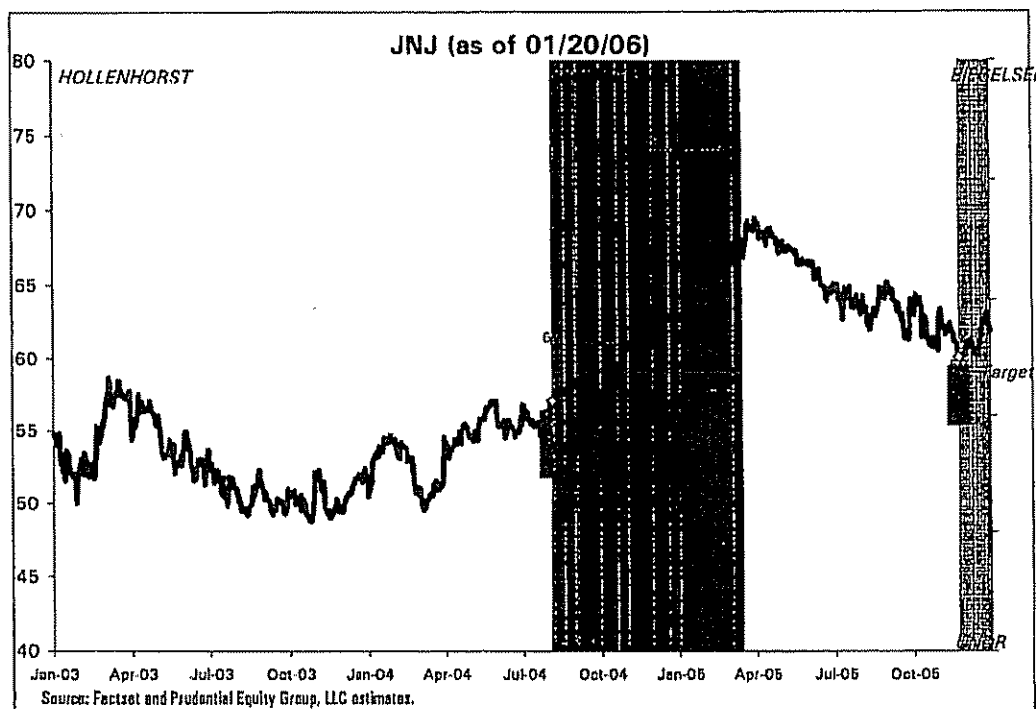
The methods used to determine the price target generally are based on future earning estimates, product performance expectations, cash flow methodology, historical and/or relative valuation multiples. The risks associated with achieving the price target generally include customer spending, industry competition and overall market conditions.

Additional risk factors as they pertain to the analyst's specific investment thesis can be found within the report.

Price History: JNJ

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Guidant Impact on JNJ Cash EPS, GAAP EPS and Growth - \$78 per Share (61% cagr)										
In Millions, Except Per Share Data										
	2005 E	2006 E	2007 E	2008 E	2009 E	2010 E	'05-'08	'05-'10	'07-'10	
Revenue Impact of GDT (\$)	\$51,185	\$53,819	\$57,263	\$60,996	\$63,778	\$68,791	6.0%	6.1%	6.3%	
JNJ Sales (ex-GDT)	\$3,549	\$3,899	\$4,479	\$5,235	\$5,942	\$6,500	13.8%	12.9%	13.2%	
Total Incremental Sales (Guid)	\$54,735	\$57,718	\$61,742	\$66,231	\$69,720	\$75,290	6.6%	6.6%	6.8%	
Pro-Forma Y-Y %	5.5%	7.0%	7.3%	7.3%	5.3%	8.0%				
JNJ Growth Ex-GDT	8.1%	5.1%	6.4%	6.5%	4.6%	7.9%				
Sales Growth Impact of GDT		0.3%	0.6%	0.8%	0.7%	0.1%				
Profit Impact										
Total Incremental Operating Profit	832	1,254	1,591	1,860	1,860	2,132				
Merger Synergies	0	0	0	0	0	0				
GDT Other Expenses	12	23	41	53	53	53				
Profit w/Synergies and GDT Other Expense	820	1,231	1,551	1,807	1,807	2,079				
After Tax GDT Income	623	936	1,178	1,373	1,373	1,580				
Impact on JNJ Interest Income - After Tax	-458	-439	-409	-373	-373	-329				
Net Impact on JNJ Net Profit	165	497	769	1,000	1,000	1,251				
CAGR										
Pre GDT JNJ EPS	3.49	3.74	4.09	4.38	4.52	4.98	7.9%	7.4%	6.8%	
JNJ Cash EPS with GDT		3.60	4.04	4.40	4.61	5.12	8.0%	8.0%	8.3%	
GDT Impact on Cash EPS		-0.14	-0.05	0.02	0.09	0.14				
Amort of Intang. Per Share (Non-Cash)		(0.16)	(0.16)	(0.16)	(0.16)	(0.16)				
JNJ GAAP EPS with GDT		\$3.44	\$3.87	\$4.23	\$4.44	\$4.96				
GDT Impact on JNJ GAAP EPS		(0.30)	(0.21)	(0.14)	(0.08)	(0.02)				
Growth Impact of GDT										
Pre GDT JNJ EPS Y-Y		7.1%	9.4%	7.1%	3.3%	10.2%				
JNJ EPS ex-Amort of GDT Intangibles		3.2%	12.2%	9.0%	4.8%	11.2%				
Impact of GDT ex-Amort. of Intangibles		-3.9%	2.8%	1.8%	1.5%	1.0%				
JNJ GAAP EPS Y-Y with GDT Intangibles		-1.5%	12.7%	9.3%	4.9%	11.6%				
GDT Impact on GAAP EPS Growth		-8.6%	3.3%	2.2%	1.7%	1.4%				
A Actuals										
E Prudential Equity Group Estimates										
Source: Prudential Equity Group, LLC, and Company Reports										
Assumes JNJ shares are worth \$62.00										

Guidant Impact on JNJ Cash EPS, GAAP EPS and Growth - \$90 per Share (66% c)											
In Millions, Except Per Share Data											
	2005 E	2006 E	2007 E	2008 E	2009 E	2010 E	'05-'08	'05-'10	'07-'10	CAGR	
Revenue Impact of GDT (\$)	\$51,185	\$53,819	\$57,263	\$60,996	\$63,778	\$68,791	6.0%	6.1%	6.3%		
JNJ Sales (ex-GDT)	\$3,549	\$3,899	\$4,479	\$5,235	\$5,942	\$6,500	13.8%	12.9%	13.2%		
Total Incremental Sales (Guid)	\$54,735	\$57,718	\$61,742	\$66,231	\$69,720	\$75,290	6.6%	6.6%	6.8%		
Total JNJ-GDT Pro Forma S	5.5%	7.0%	7.0%	7.3%	5.3%	8.0%					
Pro-Forma Y-Y %	8.1%	5.1%	6.4%	6.5%	4.6%	7.9%					
JNJ Growth Ex-GDT	0.3%	0.6%	0.6%	0.8%	0.7%	0.1%					
Sales Growth Impact of GDT											
Profit Impact											
Total Incremental Operating Profit	832	1,254	1,591	1,860	2,132						
Merger Synergies	0	0	0	0	0						
GDT Other Expenses	12	23	41	53	53						
Profit w/Synergies and GDT Other Expe	820	1,231	1,551	1,807	2,079						
After Tax GDT Income	623	936	1,178	1,373	1,580						
Impact on JNJ Interest Income - After T	-596	-577	-547	-511	-467						
Net Impact on JNJ Net Profit	27	359	632	862	1,113						
CAGR											
2005 E	2006 E	2007 E	2008 E	2009 E	2010 E	'05-'08	'05-'10	'07-'10			
Pre GDT JNJ EPS	3.49	3.74	4.09	4.38	4.52	4.98	7.9%	7.4%	6.8%		
JNJ Cash EPS with GDT		3.56	3.99	4.35	4.56	5.08	7.7%	7.8%	8.4%		
GDT Impact on Cash EPS		-0.18	-0.09	-0.02	0.04	0.10					
Amort of Intang. Per Share (Non-Cash)		(0.16)	(0.16)	(0.16)	(0.16)	(0.16)					
JNJ GAAP EPS with GDT		\$3.39	\$3.83	\$4.19	\$4.40	\$4.92					
GDT Impact on JNJ GAAP EPS		(0.34)	(0.26)	(0.18)	(0.12)	(0.06)					
Growth Impact of GDT											
Pre GDT JNJ EPS Y-Y		7.1%	9.4%	7.1%	3.3%	10.2%					
JNJ EPS ex-Amort of GDT Intangibles		2.0%	12.3%	9.1%	4.8%	11.3%					
Impact of GDT ex-Amort. of Intangibles		-5.2%	2.9%	1.9%	1.5%	1.1%					
JNJ GAAP EPS Y-Y with GDT Intangibi		-2.7%	12.9%	9.4%	5.0%	11.7%					
GDT Impact on GAAP EPS Growth		-9.8%	3.5%	2.3%	1.7%	1.5%					
A Actuals											
E Prudential Equity Group Estimates											
Source: Prudential Equity Group, LLC, and Company Reports											
Assumes JNJ shares are worth \$62.00											

St. Jude Impact on JNJ Cash EPS, GAAP EPS and Growth - \$62 Per Share (60% Cash

In Millions, Except Per Share Data										CAGR			
	2005 E	2006 E	2007 E	2008 E	2009 E	2010 E	'05-'08	'05-'10	'07-'10				
Revenue Impact of STJ (\$MM)	\$51,185	\$53,819	\$57,263	\$60,996	\$63,778	\$68,791	6.0%	6.1%	6.3%				
JNJ Sales (ex-STJ)	\$2,922	\$3,543	\$3,930	\$4,369	\$4,883	\$5,456	14.3%	13.3%	11.6%				
Total Incremental Sales (STJ)	\$54,108	\$57,361	\$61,193	\$65,365	\$68,661	\$74,247	6.5%	6.5%	6.7%				
Total JNJ-STJ Pro Forma Sales													
Pro-Forma Y-Y %													
JNJ Growth Ex-STJ	8.1%	5.1%	6.4%	6.5%	4.6%	7.9%							
Sales Growth Impact of STJ			0.3%	0.3%	0.5%	0.3%							
Profit Impact													
Total Incremental Operating Profit		976	1,104	1,229	1,385	1,572							
Merger Synergies		200	200	200	200	200							
STJ Other Expense		27	4	0	-4	-10							
Profit w/Synergies and STJ Other Expenses		1,149	1,300	1,429	1,590	1,782							
After Tax STJ Income		850	962	1,057	1,176	1,319							
Impact on JNJ Interest Income - After Tax		-489	-465	-439	-410	-378							
Net Impact on JNJ Net Profit		361	497	619	766	941							
Pre STJ JNJ EPS													
2005 E	3.49	3.74	4.09	4.38	4.52	4.98	7.9%	7.4%	6.8%				
JNJ Cash EPS with STJ		3.67	4.05	4.36	4.55	5.04	7.7%	7.5%	7.6%				
STJ Impact on Cash EPS		-0.06	-0.04	-0.01	0.03	0.06							
Amort of Intang. Per Share (Non-Cash)		(0.14)	(0.14)	(0.14)	(0.14)	(0.14)							
JNJ GAAP EPS with STJ		\$3.53	\$3.91	\$4.23	\$4.41	\$4.90							
STJ Impact on JNJ GAAP EPS		(0.20)	(0.17)	(0.15)	(0.11)	(0.08)							
Growth Impact of STJ													
Pre STJ JNJ EPS Y-Y		7.1%	9.4%	7.1%	3.3%	10.2%							
JNJ-STJ EPS ex-Amort of STJ Intangibles		5.3%	10.3%	7.8%	4.2%	10.9%							
Impact of STJ ex-Amort. of Intangibles		-1.9%	0.9%	0.7%	0.9%	0.7%							
JNJ GAAP EPS Y-Y with STJ Intangibles		1.4%	10.7%	8.1%	4.3%	11.2%							
STJ Impact on GAAP EPS Growth		-5.7%	1.3%	0.9%	1.1%	1.0%							
Assumes STJ bought at \$62 per share (15% Premium to January 13 Close)													
Assumes JNJ shares are worth \$62.00													
A Actuals													
E Prudential Equity Group Estimates													
Source: Prudential Equity Group, LLC, and Company Reports													

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Exhibit G

January 23, 2006



HEALTHCARE INDUSTRY NOTE

The Game May Be Far from Over

Disclosure Information: Please see pages 5 - 12 of this report for important disclosure information.

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We have had conversations with Johnson & Johnson (JNJ) and Boston Scientific (BSX) and others recently that lead us to believe that the Guidant (GDT) game is far from over. Both companies seem intent on winning the battle for GDT, even to the extent of being 'nice' to sell side analysts. Our takeaway message from these conversations has been that both sides believe there is information to share that can bolster the argument for its being a better suitor for GDT.

JNJ, for example, reminded us that the analysis that BSX presented as to its valuation included price objectives that did not assume the deal had taken place. That is certainly true of our \$42 price objective, which is built on our beliefs about the dynamics of the drug eluting stent market and BSX's potential pipeline of products (moving to the right in time and leaving some unsuccessful projects behind to be sure, assuming its deal with GDT goes through). Suffice it to say, we were glad that BSX did not just use our Price Objective, but averaged it with others.

We were also reminded by JNJ that it had three patents related to '-limus' compounds that it thought precluded any other company from using such a compound on a stent. We were only given two patent numbers (6776796 and 6585764), and, sure enough, both have to do with using any '-limus' on a stent. We have not vetted these patents, but they did seem quite broad in their language. When we spoke to BSX management about them, we were told neither GDT nor Abbott (ABT) seemed to be concerned about them, and that their broad

language may make them non-defensible. As we said, we have not vetted them yet

Here Are Our Initial Thoughts for Potential EPS, Assuming Things Go Through as BSX Has Planned

As for our conversation with BSX, we were surprised, somewhat, by the conservative assumptions it was making on stent market share (it was trying to keep to Street assumptions) and especially on GDT high voltage market share (we had been presuming, as has the Street, a faster ramp to normalcy). BSX is assuming that GDT only will have 26% share exiting '07, 25% in mid-'07 and 24% in 4Q06. Because of this we are assuming the company earns \$0.90 in '06, \$1.35 in '07, \$1.80 in '08 and \$2.35 in '09 on a pro forma basis, assuming the BSX/GDT merger goes through as planned. We believe the company's internal estimates are lower than these. We discuss how we derived these estimates in more detail later on in this piece

We also would like to remind investors that this analysis and all subsequent analysis on this piece are based on the assumption that BSX does indeed merge with GDT at the \$80 price recently submitted by BSX. JNJ has yet to respond to this new bid by BSX and it may do so. As a result, investors should view this analysis as speculation based on what we know at this time. **Since this is speculation, we are maintaining our price objective and estimates at this time as we have no assurances that BSX will end up with GDT.** It is still a pretty dynamic atmosphere out there in our view.

Additional Synergies with BSX/GDT? Perhaps. BSX also told us that there were more potential synergies than it had initially expected. It has said that it expected \$400 million in synergies, \$200 million from the GDT side and \$200 million from its side, mainly from reducing corporate overhead and only having to have 1.2x the international

infrastructure that it currently has. It has also determined that there are between \$50 million and \$100 million of manufacturing savings that can be realized as well (especially in inspection, scrap and waste). We are not surprised by this. Our experience at GDT was that manufacturing efficiency, while taken seriously, was not taken as seriously as it has been at BSX.

As far as the arrangements with ABT is concerned (ABT, if BSX ends up with GDT, would purchase GDT's vascular business and share rights to GDT's drug eluting stent program. It also would own a portion of BSX, approximately 4%), it appears that ABT was the only true candidate for the rapid exchange technology or the larger deal that BSX is proposing. This would imply that the FTC is probably agreeable to the plan being offered, so it is more of a matter of time than worrying about the structure of the planned acquisition. We do believe that a definitive offer will likely have to be in place prior to the deal being closed. We also think that it will be late 2008/early 2009 before we see a combination product in the market.

Interesting times these.

Our Numbers Analysis, at Least on a Theoretical Basis

Now that it is BSX's turn at bat in the battle for GDT (JNJ may be heard from before Wednesday), we thought we would take a look at what BSX's value might be after any such merger. However, **investors should keep in mind once again that this exercise is theoretical**, as GDT has yet to recommend BSX's bid and we have not heard back from JNJ who, again, could come back with a new bid itself. BSX did give some level of guidance of what it might expect to see in terms of EPS after a potential merger when it bid \$72 per share for GDT. At that time, BSX stated that we could expect EPS to be in a range of \$1.50 to \$1.66 in 2007 and \$1.98 to \$2.18 in 2008.

A lot has changed since that time, however due to BSX's \$80 bid for GDT. While we think BSX wisely sold some equity to Abbott (ABT) in its latest bid, which resulted in less debt being accumulated, there still should be some additional incremental debt it has taken on (around \$200 million) and potential EPS dilution from those new shares being sold to ABT.

Back to the Pre-Taxus Days in Terms of Expense Control?

However, in our subsequent discussions with the company, it indicated a willingness to return to "pre-

Express/Taxus" spending disciplines, assuming that it succeeds in its efforts to acquire GDT. Remember before the Express stent (the bare metal platform that BSX developed internally before the DES era), BSX was suffering from an extended period of market share losses (down to 8% of the market by our reckoning) and lackluster top line growth.

We think that cost control at this point is important. During past analyst meetings BSX indicated that it wanted to keep its after tax margins below 30% as it believed that it had a number of projects it could invest in both internally and externally (and it mentioned at the time, we think correctly, that investors would not reward it for a relatively high after tax margin). Our question is how deeply will BSX reign in costs assuming that its operations are already relatively efficient, as evidenced by operating margins often in excess of 30%? After speaking with the company on Friday, it is apparent that it does intend to slow down expenditures, because, as the management put it, now that we would have GDT's pipeline and R&D efforts, we may be able to slow down or stop expenditures related to longer-term projects. We should all remember that BSX has been spending approximately \$600 million or more on milestone payments and new technology projects in addition to its in-house R&D expenditures. With a new focus, having acquired GDT, these projects will be reviewed and some of them most likely terminated.

We May See Dilution Until FY10, in This Scenario

Regardless of the synergies the company finds in these R&D programs, BSX's EPS should be diluted until FY10, at least according to our analysis and our assumptions so far. We are assuming that in the DES market that BSX retains its entire market share that we assumed it would get before the merger (approximately 30%) and we layered on top of that a portion of what we assumed would be GDT's market share. **This analysis and all subsequent analysis in this piece, again, is predicated on BSX succeeding in obtaining GDT, which we think is not a sure thing** as we have not definitively heard from JNJ as of yet.

Going into more detail, we originally assumed that GDT would also achieve approximately 30% of the DES market by the end of the decade. Taking that figure we assumed that BSX and ABT would split 40% of that market share each, with the remainder going to JNJ, due to continuity of JNJ's operations and marketing teams (sorry, MDT). The company has told us that it is assuming that two-thirds of the market share will be incrementally derived, and

one-third from cannibalization. The numbers work out to be almost equivalent. We are going to stick with our analysis. It's easier on the eyes

We further assumed that BSX would have most of its integration issues behind it by late FY08 to early FY09 with its operating margins starting to return to normalcy (30%+). The company is actually more conservative and assumes that it will not reach that goal until close to FY10. We are also assuming that GDT's CRM group slowly returns to close to a 30% market share range in high voltage in the United States by the end of the decade. However, due to GDT related debt, integration costs and additional shares that BSX has offered, it emerges from earnings dilution around FY10 in our model. Preliminarily, we assume that BSX's pro-forma earnings may approximate \$0.90 for FY06, \$1.35 for FY07, \$1.80 for FY08 and \$2.35 for FY09. Once again, this is predicated on the assumption that BSX acquires GDT, and all of this analysis may change quickly if JNJ comes in with a competing bid.

Here's Our Initial Take on a Theoretical Valuation, But the Game Might Not Be Over Yet. Keeping those assumptions and qualifiers in mind, recently our peer group average for BSX (MDT, EW, STJ) was trading at a one year forward multiple of 25.6x. The question we believe worth asking, is what should be the discount to that multiple? Using that average with no discount leads us to a valuation of \$35 per share, utilizing our preliminary FY07 estimate. We decided to use FY07 as opposed to the one year forward (FY06) as FY07 would be the first full fiscal year with GDT under its belt as well as the first year it may begin to move toward normalcy. However, we do believe that BSX should receive some discount due to the potentially higher short-term financial risk the company might face. The problem is that we cannot think of any recent acquisitions of this size and scope among equals that is dilutive over the course of a couple years in this or any other industry. Therefore any number we pick as a discount rate would be somewhat arbitrary.

Since we were unsure on what discount to that multiple should be, we decided to create a table of discount values to determine a valuation range and then make an more educated estimate on what a potential valuation might be using our recent comp group EPS multiple of 25.6x as a base.

EPS Ests	Discount Rates			
	10%	20%	30%	40%
\$1.15	\$26.50	\$23.55	\$20.61	\$17.66
\$1.25	\$28.80	\$25.60	\$22.40	\$19.20
\$1.35	\$31.10	\$27.65	\$24.19	\$20.74
\$1.45	\$33.41	\$29.70	\$25.98	\$22.27
\$1.55	\$35.71	\$31.74	\$27.78	\$23.81

Source: A.G. Edward theoretical estimates.

Using the middle portion of this table as a proxy for potential outcomes, we see a range of potential values of \$30 to \$22 per share. This fits in within our preliminary pro-forma discounted cash flow analysis of approximately \$28 per share. In that analysis, we used all of the EPS assumptions listed above as well as weighted average cost of capital of 12.0%, an implied market risk for the shares of 10.5% (our large cap universe range is 7.5% to 11.0%) and a long-term growth rate of 12%.

However, we would also like to stress that this is a preliminary analysis. We expect to see and hear more from BSX, GDT and possibly JNJ in the coming days. Our intention is to give investors an idea of what might be, given events could change very quickly. Importantly, we are sticking with our price objective for BSX of \$42 per share and our current estimates as we do not believe this saga is near completion at this time.

Boston Scientific (BSX – \$23.34 – Buy/Aggressive) Valuation

We use a three-stage discounted cash flow model, which leads us to a price objective of \$42 per share. Our weighted average cost of capital was 11.3%. Our market risk premium is 9%. We assumed a free cash flow growth rate of 11.75% for 10 years after our detailed cash flow model ends in 2010 and assume a growth rate of 4% thereafter. On a P/E basis, BSX's one-year forward P/E five-year average is 28.8x with a range of 70.7x to 12.0x. Based upon our FY06 estimate of \$1.82 and our price objective of \$42, we have a target P/E value of 23.0x, a discount to its five-year average, but appropriate in our opinion as we think BSX has a good long-term pipeline.

BSX Risks To Valuation

Risk to achieving our price objective include unanticipated market share losses in the drug-eluting stent market (e.g., new competitive products being more successful than we anticipate, product recalls, etc.), new products not being successfully brought to market or not experiencing sales levels as high as we anticipate, regulatory risk (e.g., reimbursement and regulatory approval), ongoing

litigation risk and the highly competitive markets in which the company competes.

Guidant (GDT – \$76.00 – Hold/Speculative) Valuation

We use a three stage discounted cash flow model for our valuation. Our discount rate on our future cash flows, which is the weighted average cost of capital, we are using is 12.1%. This and other assumptions lead us to believe GDT is at fair value. Based upon our FY06 estimate of \$1.70 per share, GDT is now trading at a P/E multiple of 44.8x.

GDT Risks To Valuation

The ongoing issues and uncertainties we have seen in the stent business are the major risks for Guidant. Others include acquisition risks, slower than expected uptake of CHF devices, new technology not only from direct competitors, but also from other sectors as well such as Pharma, regulatory risk, reimbursement risk and litigation risk.

Johnson & Johnson (JNJ – \$61.19 – Hold/Conservative) Valuation

We utilize a three-stage discounted cash flow analysis for our valuation methodology. Our weighted average cost of capital assumption at the time of analysis was 10.4%, we assumed a free cash flow growth rate of 9.0% for 10 years after our detailed forecasts embedded in our model end in FY10, and 4.0% thereafter. These and other assumptions lead us to believe that the shares are at a level that represents what we would consider fair value. On a P/E basis, JNJ's two-year forward P/E five-year average is 20.0x with a range of 27.7x to 15.2x. Based upon our FY06 estimate of \$3.80, JNJ is currently trading at a P/E (at a recent price of \$61.19 per share) of 16.1x. We believe that a multiple at the lower end of the range is justified due to competition in the drug-eluting stent marketplace, and potential and existing generic competition in some product lines in pharma.

JNJ Risks To Valuation

Johnson & Johnson may see greater competition than expected in the drug-eluting stents market in

the United States, and new drug-eluting stent products from competitors in Europe. The Pharma pipeline may be weaker than expected, and there may be increased competition from generic manufacturers.

Abbott Labs (ABT – \$40.51 – Buy/Aggressive) Valuation

We utilize a three-stage discounted cash flow analysis for our valuation methodology. Our weighted average cost of capital assumption is 11.5% and our risk premium assumption is 9%. Our out year operating cash flow growth assumption is 11.0% for ten years (2011-2020)-right in the middle of the largest of our large-cap group. These and other assumptions lead us to our price objective of \$46 per share. On a P/E basis, using our \$2.70 FY06 EPS estimate, and our \$46 price objective the multiple is 17.0x. This compares to a five-year historical two-year forward P/E average of 18.3x, with a range of 13.4x to 25.2x. We feel that our implied target multiple, which is close to its historical average, is justified due to uncertainty concerning generic competition, but offset by good potential we see in Medical Products. Therefore, being close to the middle seems like a good place to be.

ABT Risks To Valuation

Risks to achieving our price objective include the fact that Abbott's pharmacological pipeline may not be as robust as we have assumed, sales of its key products (such as Humira) may not be as strong as we anticipate and it participates in highly competitive and regulated markets.

Analyst Certification Statement

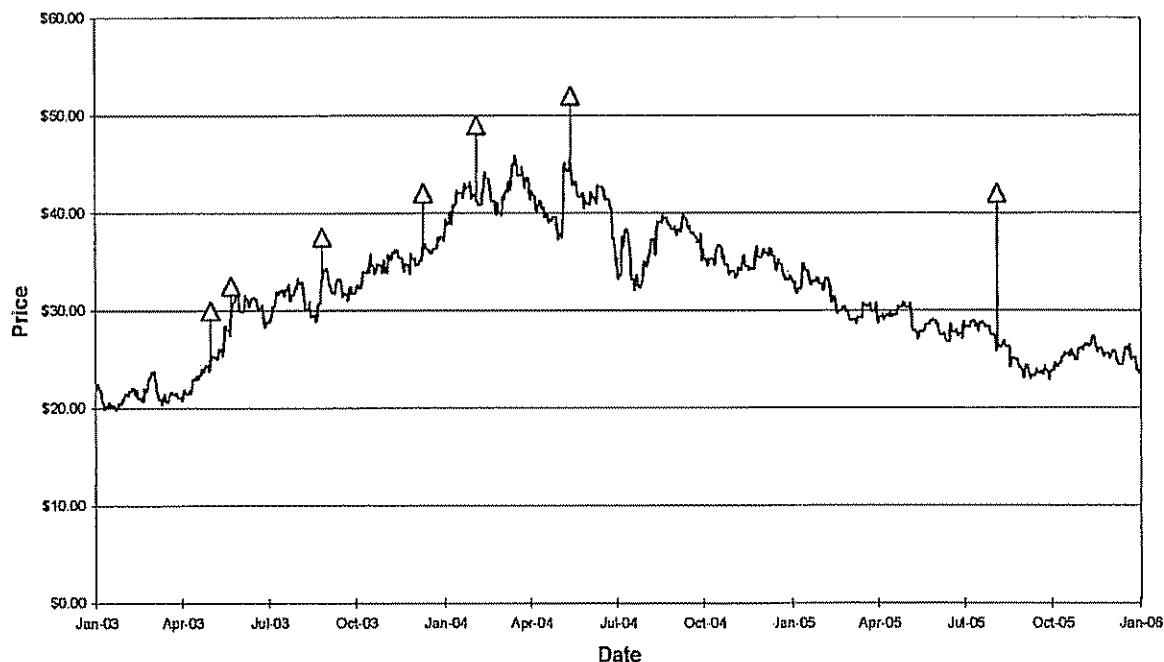
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All prices from intraday on 1/23/06.

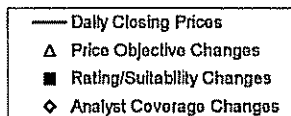
BOSTON SCIENTIFIC

January 21, 2006
Buy/Aggressive
 BSX/NYSE/\$23.59

Price Objective: \$42.00



Pricing sources: Factsot and IDS1

**PRICE OBJECTIVE (PO) CHANGES ***

Date	Closing Price	PO	Date	Closing Price	PO	Date	Closing Price	PO
		25.00	09/16/2003	33.25	37.50	06/02/2004	44.70	52.00
05/21/2003	25.04	30.00	12/30/2003	36.54	42.00	08/24/2005	26.38	42.00
06/11/2003	29.88	32.50	02/24/2004	41.27	49.00			

* NA: Positive rating removed; no price objective supplied.

RATING/SUITABILITY CHANGES

Date	Closing Price	Rating/Suitability	Date	Closing Price	Rating/Suitability
		Strong Buy/Aggressive			

ANALYST COVERAGE CHANGES

Analyst	From	To	Analyst	From	To
Jan D. Wald	01/18/2001				

ABT 009714

BOSTON SCIENTIFIC**January 21, 2006****Buy/Aggressive****BSX/NYSE/\$23.59****Price Objective: \$42.00**

Rating	Master List Companies	Current Rating Distribution	Investment Banking Clients	Past 12 months
				% of Investment Banking Clients *
Buy	257	36%	48	19%
Hold/Neutral	440	62%	28	6%
Sell	12	2%	0	0%

* Percentage of Investment Banking Clients on Master List by rating.

OUR 3-TIER RATING SYSTEM (12-18 month time horizon)

Buy: A total return is anticipated in excess of the market's long-term historic rate (approximately 10%). Total return expectations should be higher for stocks which possess greater risk.

Hold: Hold the shares, with neither a materially positive total return nor a materially negative total return is anticipated.

Sell: Stock should be sold, as a materially negative total return is anticipated.

RISK SUITABILITY (Relates to fundamental risk, including earnings predictability, balance sheet strength and price volatility)

Conservative: Fundamental risk approximates or is less than the market.

Aggressive: Fundamental risk is higher than the market.

Speculative: Fundamental risk is significantly higher than the market.

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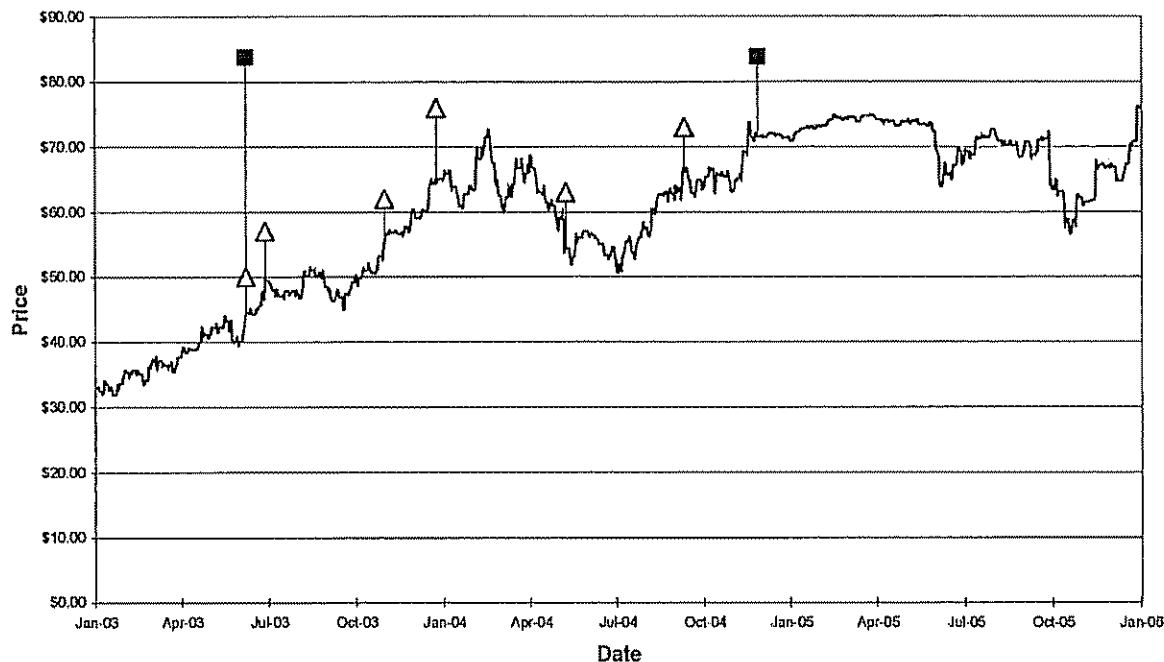
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ABT 009715

GUIDANT CORP

January 21, 2006
 Hold/Speculative
 GDT/NYSE/\$75.95



Pricing sources: Factset and IDS1

— Daily Closing Prices
 ▲ Price Objective Changes
 ■ Rating/Suitability Changes
 ◆ Analyst Coverage Changes

PRICE OBJECTIVE (PO) CHANGES *

Date	Closing Price	PO	Date	Closing Price	PO	Date	Closing Price	PO
		NA	11/20/2003	55.35	62.00	09/30/2004	66.04	73.00
06/27/2003	44.51	50.00	01/13/2004	64.28	76.00	12/17/2004	71.62	NA
07/17/2003	49.96	57.00	05/28/2004	54.34	63.00			

* NA: Positive rating removed; no price objective supplied.

RATING/SUITABILITY CHANGES

Date	Closing Price	Rating/Suitability	Date	Closing Price	Rating/Suitability
06/27/2003	44.51	Hold/Speculative Buy/Speculative	12/17/2004	71.62	Hold/Speculative

ANALYST COVERAGE CHANGES

Analyst	From	To	Analyst	From	To
Jan D. Wald	01/08/2001				

ABT 009716

GUIDANT CORP**January 21, 2006****Hold/Speculative****GDT/NYSE/\$75.95**

Rating	Master List Companies	Current Rating Distribution	Past 12 months	
			Investment Banking Clients	% of Investment Banking Clients *
Buy	257	36%	48	19%
Hold/Neutral	440	62%	28	6%
Sell	12	2%	0	0%

* Percentage of Investment Banking Clients on Master List by rating.

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Aggressive: Fundamental risk is higher than the market

Speculative: Fundamental risk is significantly higher than the market.

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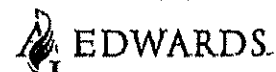
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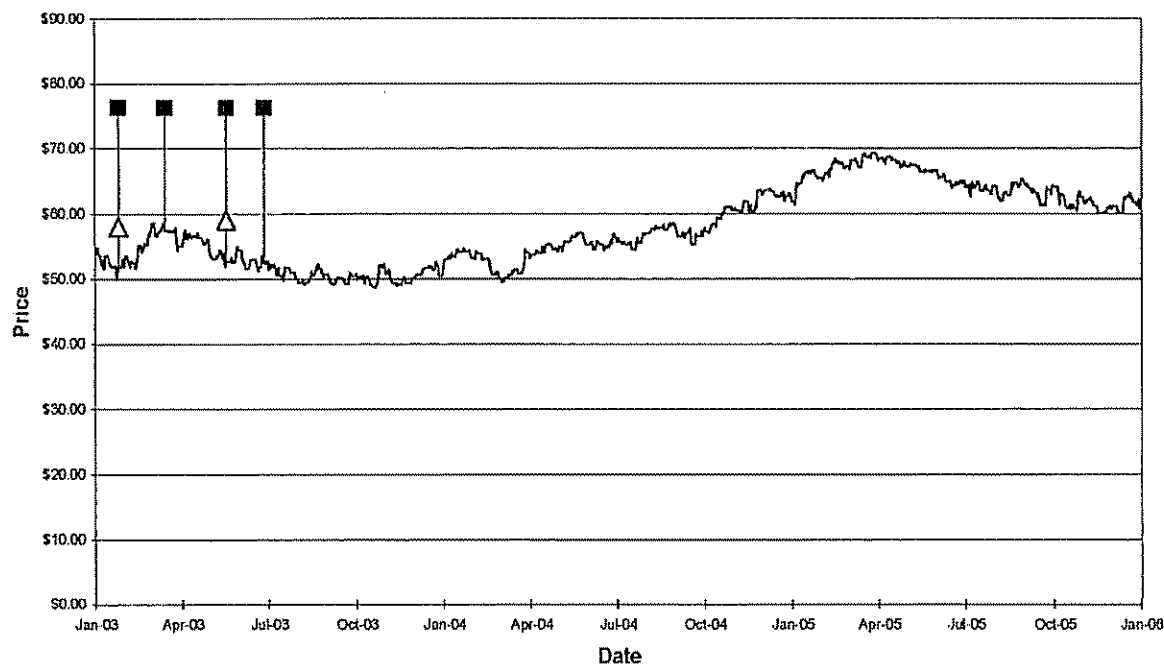
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ABT 009717

JOHNSON & JOHNSON

January 21, 2006

Hold/Conservative**JNJ/NYSE/\$60.80**

Pricing sources: Factset and IDS1

--- Daily Closing Prices
 Δ Price Objective Changes
 ■ Rating/Suitability Changes
 ◇ Analyst Coverage Changes

PRICE OBJECTIVE (PO) CHANGES *

Date	Closing Price	PO	Date	Closing Price	PO	Date	Closing Price	PO
02/14/2003	51.75	58.00	04/03/2003	57.46	NA	07/16/2003	52.60	NA
			06/06/2003	52.75	59.00			

* NA: Positive rating removed; no price objective supplied.

RATING/SUITABILITY CHANGES

Date	Closing Price	Rating/Suitability	Date	Closing Price	Rating/Suitability
02/14/2003	51.75	Hold/Conservative	06/06/2003	52.75	Buy/Conservative
04/03/2003	57.46	Buy/Conservative	07/16/2003	52.60	Hold/Conservative
		Hold/Conservative			

ANALYST COVERAGE CHANGES

Analyst	From	To	Analyst	From	To
Jan D. Wald	08/17/2001				

ABT 009718

JOHNSON & JOHNSON**January 21, 2006****Hold/Conservative****JNJ/NYSE/\$60.80**

Rating	Master List Companies	Current Rating Distribution	Past 12 months	
			Investment Banking Clients	% of Investment Banking Clients *
Buy	257	36%	48	19%
Hold/Neutral	440	62%	28	6%
Sell	12	2%	0	0%

* Percentage of Investment Banking Clients on Master List by rating.

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Speculative: Fundamental risk is significantly higher than the market.

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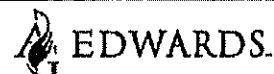
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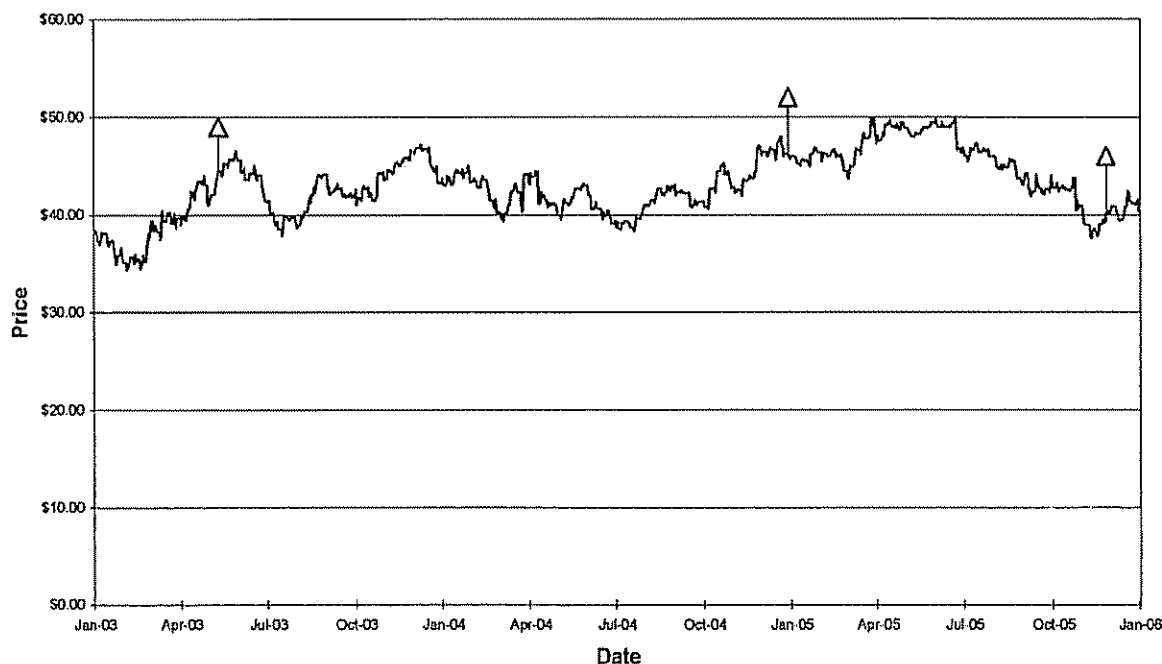
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ABT 009719

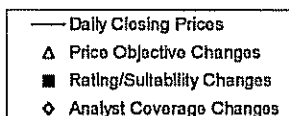
ABBOTT LABORATORIES

January 21, 2006
Buy/Aggressive
 ABT/NYSE/\$40.35

Price Objective: \$46.00



Pricing sources: Factsot and IDS1

**PRICE OBJECTIVE (PO) CHANGES ***

Date	Closing Price	PO	Date	Closing Price	PO	Date	Closing Price	PO
		46.00	01/18/2005	46.04	52.00			
05/30/2003	44.55	49.00	12/16/2005	40.17	46.00			

* NA: Positive rating removed; no price objective supplied.

RATING/SUITABILITY CHANGES

Date	Closing Price	Rating/Suitability	Date	Closing Price	Rating/Suitability
		Buy/Aggressive			

ANALYST COVERAGE CHANGES

Analyst	From	To	Analyst	From	To
Jan D. Wald	08/17/2001				

ABT 009720

ABBOTT LABORATORIES**January 21, 2006****Buy/Aggressive****ABT/NYSE/\$40.35****Price Objective: \$46.00**

Rating	Master List Companies	Current Rating Distribution	Investment Banking Clients	Past 12 months % of Investment Banking Clients *
Buy	257	36%	48	19%
Hold/Neutral	440	62%	28	6%
Sell	12	2%	0	0%

* Percentage of Investment Banking Clients on Master List by rating.

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Exhibit H



See page 8 for Analyst Certification and Important Disclosures

Multi-Company Note**Medical Supplies & Technology****An INTERESTING New Offer**

January 13, 2006

SUMMARY

Matthew J Dodds

Matthew J Dodds

Efrem Kamen

- BSX's new bid appears more focused on anti-trust issues than a higher price, which is likely to be based on intellectual property as much as timing. We don't think BSX's new offer is enough to get GDT to switch sides.
- A BSX/GDT deal may not have the freedom of passage through the FTC that is widely anticipated, as JNJ holds some key intellectual property needed to make ABT a "competitive" DES player.
- JNJ owns the IP around the use of the drug sirolimus (rapamycin) and its analogues on a stent - this includes both ABT-578 and everolimus.
- When the FTC initially approved JNJ/GDT in October, JNJ agreed to license rapid exchange and other stent rights to ABT. We suspect that the other stent rights included the IP surrounding the use of rapamycin analogues on a stent.
- Without this IP, the FTC could have concern over ABT's ability to make ZoMaxx or Xience V a viable competitor.

United States

SUMMARY VALUATION AND RECOMMENDATION DATA

Company (Ticker)	Price	Expected Returns				Rating	Div.(E)	Target	LTGR	Earnings Per Share	
		Price	Div.	Total						Current Yr	Next Yr
Abbott Laboratories- (ABT)	\$41.34	(8.1%)	2.5%	(5.5%)	Curr	3M	\$1.07	\$38.00	7%	\$2.48E	\$2.50E
					Prev	3M	\$1.07	\$38.00	7%	\$2.48E	\$2.50E
Boston Scientific- (BSX)	\$25.05	7.8%	0.0%	7.8%	Curr	2H	\$0.00	\$27.00	7%	\$1.83E	\$1.80E
					Prev	2H	\$0.00	\$27.00	7%	\$1.83E	\$1.80E
Guidant Corporation- (GDT)	\$70.40	(31.8%)	0.6%	(31.3%)	Curr	3H	\$0.40	\$48.00	15%	\$1.02E	\$1.49E
					Prev	3H	\$0.40	\$48.00	15%	\$1.02E	\$1.49E
Johnson & Johnson- (JNJ)	\$62.21	28.6%	2.1%	30.7%	Curr	1L	\$1.29	\$80.00	11%	\$3.50E	\$3.85E
					Prev	1L	\$1.29	\$80.00	11%	\$3.50E	\$3.85E

OPINION

BSX's new offer shows GDT's Board is as concerned with anti-trust as price...

After the close yesterday, Boston came back with another offer for Guidant. While this was widely anticipated, it is a bit quicker than we thought and the structure puts more of a focus on anti-trust concerns than a pricing premium. Specifically, the Boston offer of \$73 is only \$1 higher than the last offer and is still equally split between stock and cash. We felt Boston would go to \$76 with its follow up bid on the chance that JNJ was "maxed" at \$68. In addition to the \$1 increase in price, Boston has altered its agreement on two fronts to address two apparent concerns of Guidant's Board: 1) the ability to get through the FTC, and 2) the ability to close the deal in a timely manner. To address these concerns, Boston has now

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Citigroup Global Markets



offered to divest all overlapping assets if necessary and will pay \$0.012 in cash per day (or \$4MM per day) for every day the closing slips after April 1. The second component is quite novel, and we aren't sure if this has ever been done before in a major acquisition/merger. While it may sound lucrative since the cash register rings daily, it's really quite small (\$120MM a month) in relation to the \$25B deal size.

...And could be related to JNJ's IP around using limus compounds on a stent...

The interesting new features of Boston's offer implies that Guidant's Board is more concerned with anti-trust issues than the investment community has realized. Our recent work in the area suggests there may be one major issue that has been overlooked to date – JNJ's IP position on using sirolimus (rapamycin) and its analogues on a stent. JNJ licensed rapamycin from Wyeth but also has its own patents that cover the use of rapamycin and rapamycin analogues on a stent. These patents include the '796 patent filed in May 2001 and the '536 patent filed in April 2003. The patents have never been challenged or enforced because no other company has launched a limus-based drug-eluting stent in the US, but are likely to eventually lead to litigation. While we have not done specific research on the strength of the patents, the claims appear to somewhat broadly cover the use of rapamycin on a stent to treat restenosis.

What makes this issue interesting is that JNJ is likely to have offered a license to these patents along with rapid-exchange to Abbott since ABT-578 (the drug Abbott uses for ZoMaxx) is a rapamycin analogue. If this is correct, it means that the FTC required this access to ensure that Abbott would not face litigation from JNJ when it eventually enters the US market.

...Which would remain an issue with Boston's new offer..

In the Boston deal for Guidant, neither Boston nor Abbott would garner access to the limus patents so another competitive stent entrant may not technically be "created" with this deal. (It could be argued that Guidant didn't have access to these patents before the JNJ offer, but if the FTC determined it was an issue in its JNJ/GDT review, it's on the map.) Hence, while the Boston/Abbott deal looks quite a bit more comprehensive than the JNJ/Abbott deal, the importance of the limus patent rights appear to have been underestimated.

...Along with some other potential snags...

While Boston is now saying it will divest all required assets – which would presumably include dropping the "shared" rights to everolimus – this would require another "agreement" with Abbott since the current one does not include this scenario. It was also noted by the *Wall Street Journal* that Boston's last trip to the FTC was ugly as its acquisition of Cardiovascular Imaging Systems included an agreement with Hewlett Packard that the FTC felt was not honored. Finally, Boston has said little about EU anti-trust clearance, which may not be on fast-track status given that Boston and Guidant have more overlap and the EU authorities raised several product issues between JNJ and Guidant that the FTC did not raise.

...So the bottom line on the new offer is: we just don't think it's enough.

Last night, Guidant's Board noted that it will look at and respond to the new offer by Boston Scientific. Even with the new components of the Boston offer, we don't think Guidant's Board will get comfortable enough with the aforementioned anti-trust issues and the extra \$1. Boston is demanding that Guidant's Board respond by 4 p.m. EST today (which is ironically Friday the 13th). If Guidant doesn't take the offer (80%), Boston could still go higher on price since Guidant's Board appeared comfortable to go with Boston earlier this week when the spread was \$8. If Guidant does take Boston's new offer (20%), it's hard to



say what JNJ will do, especially given the fact that we have been incorrect on JNJ's last three moves relating to Guidant.

QUARTERLY ESTIMATES PER SHARE DATA

Ticker	Period	Current Year		Next Year		Next Year + 1	
		Current	Previous	Current	Previous	Current	Previous
ABT (FYE Dec)	1Q	\$0.58A	\$0.58A	\$0.58E	\$0.58E	NA	NA
	2Q	\$0.58A	\$0.58A	\$0.62E	\$0.62E	NA	NA
	3Q	\$0.58A	\$0.58A	\$0.60E	\$0.60E	NA	NA
	4Q	\$0.74E	\$0.74E	\$0.70E	\$0.70E	NA	NA
	Year	\$2.48E	\$2.48E	\$2.50E	\$2.50E	\$2.62E	\$2.62E
BSX (FYE Dec)	1Q	\$0.51A	\$0.51A	\$0.47E	\$0.47E	NA	NA
	2Q	\$0.48A	\$0.48A	\$0.45E	\$0.45E	NA	NA
	3Q	\$0.42A	\$0.42A	\$0.42E	\$0.42E	NA	NA
	4Q	\$0.42E	\$0.42E	\$0.46E	\$0.46E	NA	NA
	Year	\$1.83E	\$1.83E	\$1.80E	\$1.80E	\$1.99E	\$1.99E
GDT (FYE Dec)	1Q	\$0.65A	\$0.65A	NA	NA	NA	NA
	2Q	\$0.63A	\$0.63A	NA	NA	NA	NA
	3Q	\$0.28A	\$0.28A	NA	NA	NA	NA
	4Q	\$0.26E	\$0.26E	NA	NA	NA	NA
	Year	\$1.82E	\$1.82E	\$1.49E	\$1.49E	\$2.42E	\$2.42E
JNJ (FYE Dec)	1Q	\$0.97A	\$0.97A	\$1.04E	\$1.04E	NA	NA
	2Q	\$0.93A	\$0.93A	\$1.01E	\$1.01E	NA	NA
	3Q	\$0.87A	\$0.87A	\$0.97E	\$0.97E	NA	NA
	4Q	\$0.74E	\$0.74E	\$0.83E	\$0.83E	NA	NA
	Year	\$3.50E	\$3.50E	\$3.86E	\$3.86E	\$4.22E	\$4.22E

VALUATION AND RISKS - COMPANIES DISCUSSED

Johnson & Johnson (JNJ - \$62.21; 1L)

Valuation

We arrive at our \$80 target price for Johnson & Johnson based on an average of three different valuations: 1) a 21x multiple off our forward 12 months (F12M) EPS forecast; 2) a TEV/2005E EBITDA target multiple of 14x; and 3) a 10-year DCF analysis.

A 21x P/E multiple represents a weighted multiple using a sum-of-the-parts analysis on JNJ's three major divisions: Pharmaceuticals (58% of operating profit), MD&D (31%), and Consumer (11%). For Pharmaceuticals, our target multiple of 20x represents a modest premium to the large-cap pharmaceutical group average of 17x, but is in line to slightly above the better-positioned franchises of Eli Lilly (21x), and Novartis (18x). Our comp group also includes companies such as Bristol Myers. The range of this comp group is from 15x-19x.

For MD&D, our target multiple of 25x represents a 10% premium to our F12M forecast for the CMTI as JNJ's business should grow 16% in 2005E, well north of the group average. The group is comprised of 17 large-cap med tech companies and includes companies such as



Medtronic, Abbott Laboratories, and Alcon. The trading range for the comp group is 15x–33x forward 12-month EPS.

For Consumer, we are forecasting a 21x multiple, which is in line with the average F12M P/E multiple the Citigroup Home & Personal Care Products Team is forecasting for the four closest comparable companies. The range of the comps group is 18x–21x and includes companies such as Avon Products, Procter & Gamble, and Colgate-Palmolive.

For our TEV/2005E EBITDA calculation, we use the 2004 share count and net debt, and the 2005E EBITDA to calculate the current multiple of 14x. Our TEV/EBITDA premium is based on the same factors as our Price/F12M EPS target, and we arrive at a TEV/EBITDA target price of \$78. The range of our TEV/EBITDA for the comp groups ranges from 10x to 32x 2005 EBITDA.

Johnson & Johnson Valuation Ratios

	Current	CMTI	Hos. Sup. Peers	Pharma Peers	S&P 500	Multiple Target	Target Price	Total Return
LT EPS Growth	10%	15%	13%	9%	7%			
Price/F12M EPS	17x	23x	18x	17x	18x	21x	\$78.96	26%
TEV/2004 EBITDA	11x	17x	12x			14x	\$78.08	25%
Implied DCF Value	--						\$84.15	35%
Derived Price Target							\$80.40	29%
Dividend Yield								2%
Expected Total Return								31%

Source: Citigroup Investment Research estimates

Our DCF valuation of \$84 per share is based on ten years of projected free cash flow with a 1% terminal growth rate. For an equity risk premium we used 3.8%; our adjusted beta is 0.58; and our weighted average cost of capital is 6.4%.

Risks

We rate Johnson & Johnson Low Risk based on three factors: 1) Johnson & Johnson's broad business mix in three large, defensive markets – pharmaceuticals, medical products, and consumer products – makes Johnson & Johnson the most diversified large-cap company in the health care space; 2) Johnson & Johnson is a major player in all three of its targeted markets, including the No. 1 position in the \$224 billion medical products market; and 3) Johnson & Johnson has a sizable cash hoard – over \$7 billion in net cash – and free cash flow generation currently running at roughly \$1.5 billion/quarter.

Risks to our thesis include: 1) unexpected generic competition for Levaquin, Risperdal, Aciphex, Topamax, or Procrit before 2008; 2) the inability to gain further share in the US drug eluting stent market in 2005 and 2006; 3) overly aggressive growth expectations for Natrecor, Remicade, or Topamax; 4) issues related to the Guidant merger.

Given the recent heightened scrutiny over drug-safety, there also exists the risk that any of Johnson & Johnson major pharmaceuticals could face slowing sales because of new or increased safety concerns.

Investment risks relating to the medical supplies and technology ("med tech") industry include: 1) modest pricing pressure across most major product lines; 2) a reduction in sales and EPS benefit from foreign exchange based on favorable yoy comparisons of the U.S. dollar versus the Euro and Yen declining in 2005; and 3) a strengthening US economy could lead to a negative sector rotation, as the med tech industry is non-cyclical in nature.



If the impact on the company from any of these factors proves to be greater/less than we anticipate, it may prevent the stock from achieving our target price or could cause our target price to be materially outperformed

Guidant (GDT -\$70.40; 3H)

Valuation

Our \$48 target on GDT is still based on fundamental valuation and not on the newly proposed deal terms by either JNJ or BSX. Our target is based on an average of a 22x P/E multiple off of our forward 12-month EPS estimate of \$1.46 (Q4:05 - Q3:06), a 16x TEV/2005 EBITDA multiple, and a DCF valuation.

Our P/E multiple is based on GDT trading at 22x forward 12-month earnings, which is based on a multiple that is in line to slightly below our Citigroup Med Tech Index (CMTI) of 17 large-cap companies, which also averages 22x. Our index includes companies such as Medtronic, Baxter, and Alcon. Our in-line target is based on Guidant performance over the next 12-months falling right in the average range of the group. The P/E multiples in the group range from as low as 15x forward earnings to as high as 33x forward earnings.

Our TEV/EBITDA multiple of 16x 2005 EBITDA is also roughly in line with the CMTI average of 17x. This is based on the same reasons as the in-line P/E multiple. The group TEV/EBITDA multiples in the CMTI range from 10x to 32x.

Guidant Estimated Valuation Ratios If JNJ or BSX Deal Breaks

	Current	CMTI	Cardio Peers	S&P 500	Multiple Target	Target Price	Total Return
Price/F12M EPS	34x	22x	26x	18x	22x	\$45.04	-36%
TEV/EBITDA	17x	17x	20x		16x	\$50.84	-28%
Implied DCF Value	--					\$47.81	-32%
Derived Price/Target						\$47.89	-32%
Dividend Yield							1%
Expected Total Return							-32%

Source: Citigroup Investment Research

Our DCF valuation of \$48 per share is based on ten years of projected free cash flow with a 2% terminal growth rate. For an equity risk premium we used 3.8%; our adjusted beta is 0.79; and our weighted average cost of capital is 7.2%.

Risks

We rate Guidant High Risk primarily based on four factors: 1) Risk of failure of the company's DES programs; 2) Liability surrounding EVT; 3) Additional fallout from the ICD recall; and 4) A formal SEC investigation.

Upside investment risks to our Sell rating and target price include: 1) the completion of the proposed acquisition by either Johnson & Johnson or Boston Scientific, or 2) a stronger-than-anticipated return in the ICD market.

Investment risks relating to the medical supplies and technology ("med tech") industry include: 1) modest pricing pressure across most major product lines; 2) a reduction in sales and EPS benefit from foreign exchange if favorable yoy comparisons of the US dollar versus



the Euro and Yen subside; and 3) a strengthening US economy could lead to a negative sector rotation, as the med tech industry is non-cyclical in nature.

On the contrary, shares of Guidant could fall below our target price should the company's ICD market share losses continue or should legal problems relating to the recent DOJ subpoena or the SEC investigation arise. These situations would likely cause the deal to break for a second time, which could also cause Guidant to fall below our target.

Boston Scientific (BSX- \$25.05; 2H)

Valuation

Our price target on Boston Scientific remains \$27. Our \$27 target price is based off an average of three different valuations: 1) a 15x multiple off our forward 12 months (F12M) ending 3Q:06) EPS forecast of \$1.75; 2) a TEV/EBITDA target multiple of 10x; and 3) a 10-year DCF analysis.

A 15x P/E multiple represents a 30%-35% discount our CMTI F12M group multiple of 22x and is based on a forecast of minimal EPS growth from 2005-08 and the heightened risk that TAXUS share could fall below our Street low expectations. The CMTI is comprised of 17 large-cap medical devices companies, including companies such as Johnson & Johnson, Medtronic, and Alcon. The range of the CMTI F12M P/E multiples is from 15x to 33x.

Our TEV/EBITDA target multiple of 10x is also based on Boston trading at a 30%-35% discount to the current CMTI multiple of 17x. The comp group has changed ever so slightly since our last published note, pushing our multiple target for BSX to round down from 11x to 10x. This said, the difference in value is minimal. The TEV/EBITDA range for the CMTI is from 10x to 32x current enterprise value to projected 2005 EBITDA.

Boston Scientific Valuation Ratios

	Current	CMTI	Cardio Peers	S&P 500	Multiple Target	Target Price	Total Return
Price/F12M EPS	14x	23x	31x	19x	15x	\$26.12	4%
TEV/EBITDA	10x	17x	23x		10x	\$28.62	14%
Implied DCF Value	--					\$26.31	5%
Derived Price Target						\$27.01	8%
Dividend Yield							0%
Expected Total Return							0%

Source: Citigroup Investment Research

Our DCF valuation of \$27 per share is based on 10 years of projected free cash flow with a 1% terminal growth rate. For an equity risk premium we used 3.9%, our adjusted beta is 1.51 and our WACC is 8.9%.

Risks

We rate BSX shares High Risk. Investment risks particular to Boston Scientific include:

- **Reliance on a single product line.** The expected performance of the TAXUS stent in 2005 means that 40% of sales and 50% of EPS will come from a single product line. No other large-cap med tech company has this level of sales and EPS concentrated in one product line and recent data has led to questions about the safety profile of this stent



- **Patent risk surrounding the TAXUS stent.** Boston remains in litigation with JNJ over key stent patents in the US. Boston recently lost initial jury decisions on two JNJ patents (Palmaz and Gray), but won decisions on two of its own patents (Ding and Yang). These cases are unlikely to be resolved anytime soon, but could ultimately result in a large damage award or injunctive relief.
- **Competitive ASP pressure in the DES market in excess of our forecast.** We expect US DES ASPs to decline by 5% annually through 2008. Primary DES competitor JNJ is larger and better capitalized and has already been using price to win back DES market share in the US.

We would also highlight that BSX has recently announced its intentions to bid for Guidant. A culmination of this deal could adversely provide new risk to our BSX rating in either direction, as it could cause BSX share to fall due to possible dilution or could cause share to increase in value based on improved long-term prospects for BSX.

Our High Risk rating is primarily based on the company's significant reliance on a single product line combined with the outstanding legal issues noted above.

Investment risks relating to the medical supplies and technology ("med tech") industry include: 1) modest pricing pressure across most major product lines; 2) a reduction in sales and EPS benefit from FX as favorable Y/Y comparisons of the US dollar vs the Euro and Yen subside in Q4; and 3) negative sector rotation if the US economy remains strong, as the med tech industry is non-cyclical in nature.

The above factors highlight some of the risks associated with investing in Boston Scientific's shares (for a more detailed list, please see the company's most recent 10-K filing). If any of the above-mentioned risk factors has a more negative impact on the company than we anticipate, the stock will likely have difficulty achieving our target price. Conversely, if any of these risk factors has less of an impact on the company's fundamentals, the stock could materially outperform our price target.



ANALYST CERTIFICATION

APPENDIX A-1

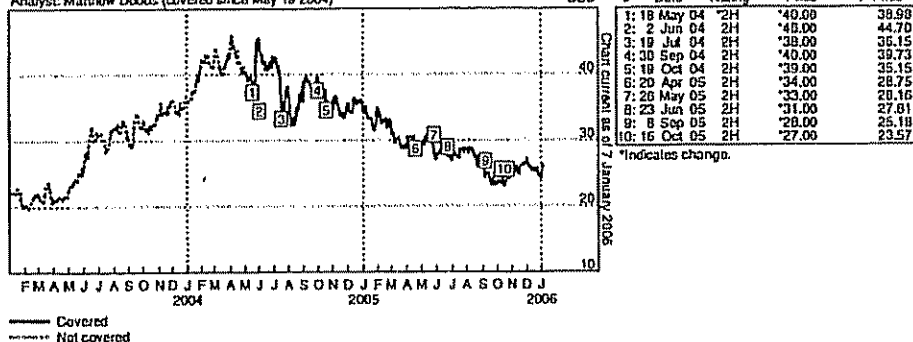
I, Matthew J. Dodds, research analyst and the author of this report, hereby certify that all of the views expressed in this research report accurately reflect my personal views about any and all of the subject issuer(s) or securities. I also certify that no part of my compensation was, is, or will be directly or indirectly related to the specific recommendation(s) or view(s) in this report.

IMPORTANT DISCLOSURES

Boston Scientific (BSX)

Ratings and Target Price History - Fundamental Research

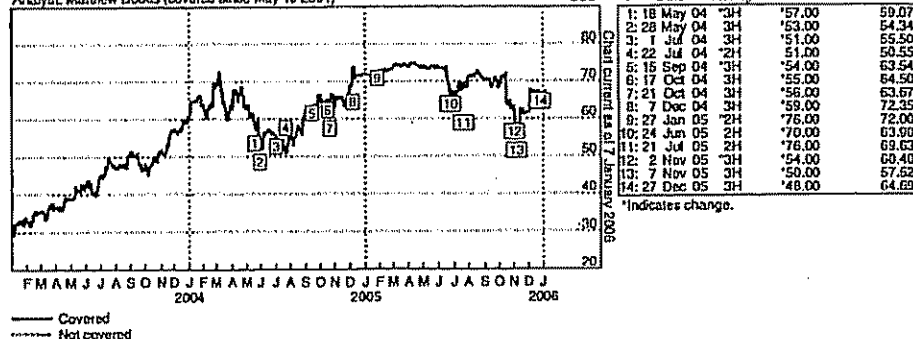
Analyst: Matthew Dodds (covered since May 19 2004)



Guidant Corporation (GDT)

Ratings and Target Price History - Fundamental Research

Analyst: Matthew Dodds (covered since May 19 2004)

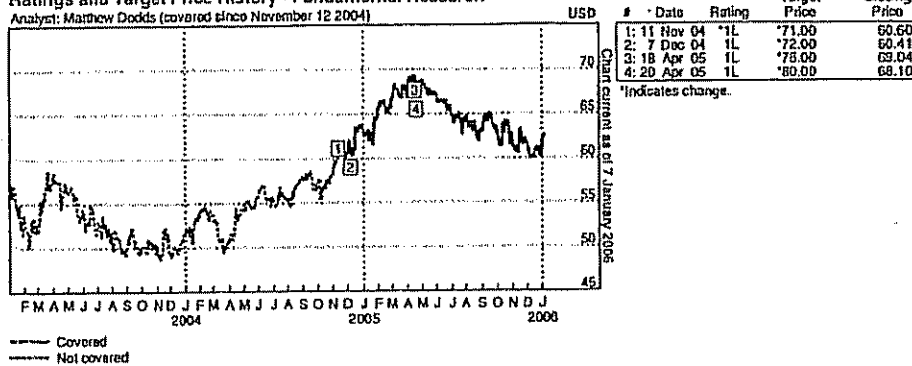




Johnson & Johnson (JNJ)

Ratings and Target Price History - Fundamental Research

Analyst: Matthew Docks (covered since November 12 2004)



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Data current as of 31 December 2005

	Buy	Hold	Sell
Citigroup Investment Research Global Fundamental Coverage (2784)	42%	41%	17%
% of companies in each rating category that are investment banking clients	47%	48%	37%
Medical Supplies & Technology - North America (9)	44%	33%	22%
% of companies in each rating category that are investment banking clients	50%	33%	50%

Guide to Fundamental Research Investment Ratings:

Citigroup Investment Research's stock recommendations include a risk rating and an investment rating.

Risk ratings, which take into account both price volatility and fundamental criteria, are: Low (L), Medium (M), High (H), and Speculative (S).

Investment ratings are a function of Citigroup Investment Research's expectation of total return (forecast price appreciation and dividend yield within the next 12 months) and risk rating.

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ADDITIONAL INFORMATION IS AVAILABLE UPON REQUEST

Exhibit I



See page 6 for Analyst Certification and Important Disclosures

Multi-Company Note**Medical Supplies & Technology****Deconstructing Xience****March 23, 2006**

Matthew J Dodds
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matthew.dodds@citigroup.com

SUMMARY

- Our work on the intellectual property (IP) challenges facing GDT's Xience stent suggests: 1) the BSX/GDT deal may not close on time and 2) ABT's purchase price for GDT's Vascular business looks excessive.
- We uncoupled the key components of Guidant's Xience drug-eluting stent and found potential IP issues on each piece.
- GDT's Vision stent appears to have a difficult roadblock against a stent patent held by Evysio that was recently licensed by MDT. This patent was recently found valid and novel by the EPO and has recently been asserted in the US.
- Everolimus will likely face two IP challenges from JNJ as both its Falotico and Wright patents claim the use of a limus analogue on a stent.
- GDT's polymer is also likely to face issues as several patents in this arena were issued before GDT even developed this polymer.

United States**SUMMARY VALUATION AND RECOMMENDATION DATA**

Company (Ticker)	Price	Expected Returns			Rating	Div.(E)	Target	LTGR	Earnings Per Share	
		Price	Div.	Total					Current Yr	Next Yr
Abbott Laboratories- (ABT)	\$44.10	(13.8%)	2.4%	(11.4%)	Curr Prev	3M 3M	\$1.07 \$1.07	7% 7%	\$2.52E \$2.52E	\$2.65E \$2.65E
Boston Scientific- (BSX)	\$23.47	(2.0%)	0.0%	(2.0%)	Curr Prev	2S 2S	\$0.00 \$0.00	7% 7%	\$1.56E \$1.56E	\$1.61E \$1.61E
Conor Medsystems- (CONR)	\$28.73	18.3%	0.0%	18.3%	Curr Prev	1S 1S	\$0.00 \$0.00	NA NA	(\$0.92)E (\$0.92)E	\$0.33E \$0.33E
Guidant Corporation- (GDT)	\$78.76	(46.7%)	0.5%	(46.2%)	Curr Prev	3S 3S	\$0.40 \$0.40	15% 15%	\$1.81E \$1.81E	\$1.30E \$1.30E
Johnson & Johnson- (JNJ)	\$61.00	31.1%	2.1%	33.3%	Curr Prev	1L 1L	\$1.29 \$1.29	11% 11%	\$3.49E \$3.49E	\$3.84E \$3.84E
Medtronic (MDT)	\$53.83	26.3%	0.6%	27.0%	Curr Prev	1L 1L	\$0.34 \$0.34	17% 17%	\$2.22E \$2.22E	\$2.54E \$2.54E

OPINION**Deconstructing Xience....We know more about the IP than the efficacy**

We have spent the past few weeks reviewing the intellectual property (IP) position of Guidant's highly-touted Xience drug-eluting stent. Our work included discussions with several companies in the drug-eluting stent space and a review by a patent expert.

This work suggests the Xience stent faces several hurdles on the intellectual property front

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Citigroup Global Markets

ABT 009748

Abbott Laboratories and Advanced Cardiovascular Systems, Inc. v. Johnson and Johnson, Inc. and Cordis Corporation DEDC C.A. No. 06-613-SLR.



that essentially cover the system through all of its primary components. While not a complete review, our analysis strongly suggests Abbott is paying a very hefty price given the IP risk and it is likely the FTC review of this IP landscape makes an early April close of the Boston/Guidant merger appear unlikely.

The stent (Vision)

Guidant's Vision stent is made of cobalt-chromium and is viewed as one of the premier bare metal stents along with Medtronic's Driver. The Vision has faced little patent opposition to date with the exception of a recent (February 10) negative decision on one patent by privately-held Medinol in the Southern district of New York. This trial is still proceeding as Guidant has challenged the patent's validity.

In Guidant's recent 10-K, another lawsuit was noted that could end up being an even bigger hurdle to Vision, especially in Europe. The case – filed in the Northern District of California on 2/16 – claims infringement by several of Guidant's balloon catheters and the Vision stent. The plaintiff in the case is Medtronic and privately-held Evysio Medical Devices, based in Vancouver.

The most interesting component of this lawsuit is the patent being asserted against the Vision – 6'858'037. This patent is owned by Evysio, but was recently licensed exclusively by Medtronic. This patent has already shown its strength in one European court and our patent work suggests the US claims are very similar.

In France, Evysio filed suit against Guidant's Vision stent soon after it was launched in 2003 seeking a preliminary injunction. At the core of this case was Evysio's patent EPO888093, which corresponds to US patent '037. On December 17, 2004, Evysio's request for a permanent injunction was not granted, but our review of the decision shows the Paris Court's decision heavily favored Evysio. While an injunction was not granted, most of Guidant's claims to dismiss the case (i.e., scope of the patent, priority date, novelty) were dismissed. In addition, the court determined that the "action on the merits seems to be serious" and Guidant was forced to post an 800,000 EUR bond pending a final decision on the case.

Since Guidant challenged the validity of the '093 patent, the case was stayed pending an Opposition Proceeding at the European Patent Office (EPO). Earlier this month, the EPO upheld the '093 patent and now the case in France can proceed. While this trial isn't likely to start until later in the year, the initial findings of the Paris court and the EPO decision put high odds on the Vision being found to infringe on the '093 patent.

Given that France is just one country in the European market (albeit the largest one) and the case may not have a final appellate decision for a couple of years, this case doesn't seem too troubling at first blush. Digging a bit deeper, we believe this case is a foreboding sign for Vision on two fronts.

First, with the favorable EPO decision and Medtronic's deep pockets, we expect Evysio and Medtronic to go after the Vision stent in several countries, including Ireland, where it is manufactured. If Vision is found to infringe in Ireland, it could lead to a lack of supply for this product in Europe.

In the US, we have compared the European '093 patent with the '037 US version and then templated the claims against the design of the Vision stent.

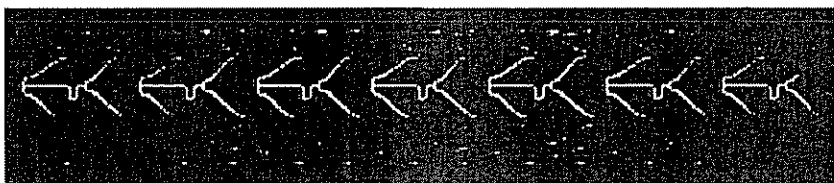
Claim 1 of the '037 patent is directed to:

An unexpanded stent comprising:



- a tubular wall having a series of undulating circumferential portions, each circumferential portion comprising alternating peaks and valleys;
- the tubular wall also having a plurality of longitudinal portions connecting said series of undulating circumferential portions to form a porous, cylindrical surface;
- a longitudinal portion connecting a peak in a first circumferential portion with a valley in a second circumferential portion adjacent to the first circumferential portion; and
- each longitudinal portion having a flexure member, said flexure member, in two dimensions, being non-sinusoidal and arcuate, each flexure member being connected to an adjacent circumferential portion with a straight strut portion which is disposed parallel to a longitudinal axis of the stent.

The Guidant Multi-link stent is reproduced below:



Based upon our legal expert's comparison of the claim language of claim 1 to the picture of the Guidant Multi-link stent, the claim language appears to literally read on the Guidant Multi-link stent. The novelty of claim 1 appears to reside in the "flexure member" which is described as "non-sinusoidal and arcuate." In the Guidant Multi-link the U-shaped member appears to correspond to the "flexure member" of the '037 patent. We have also looked at the file history of the '037 patent, and it appears that the language describing the "flexure member" was amended during prosecution of the patent.

The French decision describes claim 1 of the '093 patent, and the language of the U.S. and EPO patents are different, but claim 1 of the EPO patent also appears to be directed to the "flexure member." The EPO patent has also been amended to include a limitation directed to "laser cutting."

If we assume the '037 patent is valid (based on the favorable EPO review), the burden of proof will fall on Guidant to build a case of non-infringement. Our patent expert believes this will have to be based on prior art, which is a difficult hurdle, and suggests a 60-70% chance of success for the plaintiff.

The drug (everolimus)

Guidant obtained exclusive rights to using the drug everolimus on a stent from Novartis back in 2002. Unfortunately, obtaining rights to use the drug on a stent and holding the IP to use the drug on a stent are two entirely different things.

Over the past couple of months, potential blocking IP on using a derivative of Rapamycin, the drug JNJ uses on its Cypher stent, has surfaced. This IP originally showed up as part of JNJ's agreement with Abbott in order to receive FTC approval for the acquisition of Guidant. While JNJ originally offered Abbott what was believed to be the key to a deal – access to rapid exchange delivery system patents – Abbott apparently lobbied the FDA for two other patent portfolios owned by JNJ. These patents, broadly known as Falotico (6'776'796) and Wright (6'585'764) – were apparently deemed to be vital to the use of a limus "analogue" on a stent and both everolimus and zotarolimus (the drug used in ZoMaxx) fall under this definition of an analogue. JNJ ended up being required to license both patents to Abbott for



its ZoMaxx stent program in order to satisfy the FTC, but the deal ended up dying along with JNJ's acquisition of Guidant once Boston Scientific entered the picture.

What is interesting about this change is that Abbott is now acquiring Guidant's Xience platform alongside its ZoMaxx platform yet neither product will have access to the '796 or '764 patents. Hence, both products could be found to infringe these patents. This puts the FTC in an interesting spot as the agency was compelled to make sure Abbott received access to these patents in its approval of the JNJ/Guidant combination and will now have to be comfortable that Abbott will still be considered a viable player without access.

Of the two patents, the '796 appears to be particularly damaging as it was filed in 2001 and now has over 27 follow on patents pending with the PTO.

The polymer

Guidant finally unveiled the composition of the polymer on the Xience stent during a presentation at the ACC last week. While the name of the polymer was not provided, we did see background information on the composition – acrylic and flourinated polymers. We looked into the IP around this polymer composition and found a handful of patents granted to JNJ's polymer supplier Surmodix and a patent on flourinated polymers by Medtronic (Nolting, 6'488'701) that was filed all the way back in 1998 and issued in December 2002. We also believe JNJ's Ethicon division may have some patents around both acrylic and flourinated polymers.

It should also be noted that Guidant is likely to have trouble moving from its current durable polymer to a bioabsorbable one. As we noted in our March 14 note (*ACC 2006: DES Behind the Scenes*) concerns about late thrombosis with durable polymers appears to be driving the industry toward bioerodable polymers where Conor currently holds the lead.

While we do not believe Guidant has any version of Xience with a bioerodable polymer in the works, any work in this area could be subject to IP from its jilted partner Biosensors. Biosensors has a patent – 6'939'376 – that was just issued in September 2005 that covers immuno-suppressive drugs, including everolimus, on a stent with a biodegradable polymer. While we believe Guidant may technically have rights to this patent since its partnership with Biosensors has not been officially severed, it does appear well on its way since Biosensors Occam subsidiary sued Guidant in California on January 20 under the allegation that Guidant breached its contractual obligations.

What can happen from here

Near term, there are two events to look out for relating to these patents. First, we believe JNJ's '796 and '764 patents will need to be strongly considered by the FTC, which is likely to make Boston's plan to close the Guidant deal by April 3 unrealistic. Second, we would not be surprised to see Medtronic and Evysio file suit in Ireland shortly, which could put the EU launch of the Xience at risk.

Longer-term, the IP issues looming could be a major problem for Abbott given the amount of money that it is paying for Xience and the Street's bullish stance on Abbott's interventional cardiology prospects post the Guidant deal. Based on our analysis, Abbott would have been better off sticking with JNJ and not helping Boston win the bidding war since it would have had broader IP access and paid a much lower price. For Abbott to take this risk, we can only assume the company's expectation for either the efficacy or approval timing of its ZoMaxx platform is less optimistic than the Street's projections.



For Medtronic, the licensing of the Evysio patents could prove a key chip to barter for access to rapid exchange and/or the Lau patents.

QUARTERLY ESTIMATES PER SHARE DATA

Ticker	Period	Current Year		Next Year		Next Year + 1	
		Current	Previous	Current	Previous	Current	Previous
ABT (FYE Dec)	1Q	\$0.60E	\$0.60E	NA	NA	NA	NA
	2Q	\$0.61E	\$0.61E	NA	NA	NA	NA
	3Q	\$0.61E	\$0.61E	NA	NA	NA	NA
	4Q	\$0.70E	\$0.70E	NA	NA	NA	NA
	Year	\$2.52E	\$2.52E	\$2.65E	\$2.65E	\$2.78E	\$2.78E
BSX (FYE Dec)	1Q	\$0.42E	\$0.42E	NA	NA	NA	NA
	2Q	\$0.41E	\$0.41E	NA	NA	NA	NA
	3Q	\$0.37E	\$0.37E	NA	NA	NA	NA
	4Q	\$0.36E	\$0.36E	NA	NA	NA	NA
	Year	\$1.56E	\$1.56E	\$1.61E	\$1.61E	\$1.60E	\$1.60E
CONR (FYE Dec)	1Q	(\$0.35)E	(\$0.35)E	NA	NA	NA	NA
	2Q	(\$0.21)E	(\$0.21)E	NA	NA	NA	NA
	3Q	(\$0.20)E	(\$0.20)E	NA	NA	NA	NA
	4Q	(\$0.16)E	(\$0.16)E	NA	NA	NA	NA
	Year	(\$0.92)E	(\$0.92)E	\$0.33E	\$0.33E	\$2.15E	\$2.15E
GDT (FYE Dec)	1Q	\$0.65A	\$0.65A	\$0.30E	\$0.30E	NA	NA
	2Q	\$0.63A	\$0.63A	\$0.38E	\$0.38E	NA	NA
	3Q	\$0.28A	\$0.28A	\$0.33E	\$0.33E	NA	NA
	4Q	\$0.25A	\$0.25A	\$0.29E	\$0.29E	NA	NA
	Year	\$1.81E	\$1.81E	\$1.30E	\$1.30E	\$1.93E	\$1.93E
JNJ (FYE Dec)	1Q	\$0.97A	\$0.97A	\$1.04E	\$1.04E	NA	NA
	2Q	\$0.93A	\$0.93A	\$1.03E	\$1.03E	NA	NA
	3Q	\$0.87A	\$0.87A	\$1.00E	\$1.00E	NA	NA
	4Q	\$0.73A	\$0.73A	\$0.77E	\$0.77E	NA	NA
	Year	\$3.49E	\$3.49E	\$3.84E	\$3.84E	\$4.21E	\$4.21E
MDT (FYE Apr)	1Q	\$0.50A	\$0.50A	NA	NA	NA	NA
	2Q	\$0.54A	\$0.54A	NA	NA	NA	NA
	3Q	\$0.55E	\$0.55E	NA	NA	NA	NA
	4Q	\$0.63E	\$0.63E	NA	NA	NA	NA
	Year	\$2.22E	\$2.22E	\$2.54E	\$2.54E	\$2.94E	\$2.94E

**ANALYST CERTIFICATION****APPENDIX A-1**

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	Buy	Hold	Sell
Citigroup Investment Research Global Fundamental Coverage (2784)	42%	41%	17%
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ADDITIONAL INFORMATION IS AVAILABLE UPON REQUEST

Exhibit J

LEHMAN BROTHERS

EQUITY RESEARCH

January 30, 2006

United States of America

Healthcare

Medical Supplies & Devices

Bob Hopkins

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Boston Scientific (BSX - \$ 23.15) 1-Overweight

Company Update

BSX: The Risks - Part 1

Investment Conclusion

- Over the course of this week we will be writing a series of notes highlighting four key risks facing BSX: intellectual property or patent risk, legal and legal liability risk, regulatory risk and integration risk. Each individual note will explore a different risk with today's note focusing on intellectual property risk.

Summary

- The purpose of these notes is to provide investors with more information to assess the risk profile of BSX as BSX's valuation and pending acquisition of GDT have created significant interest in the stock.

EPS (\$) (FY Dec)

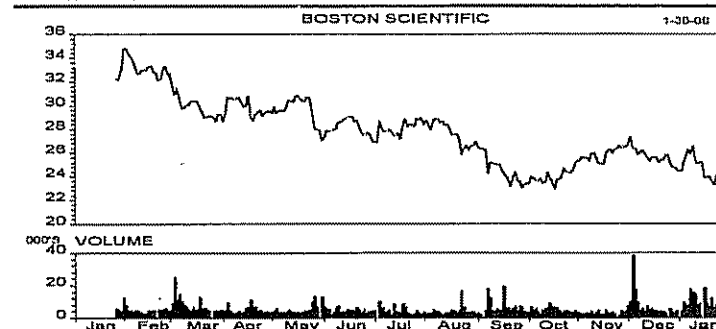
	2004		2005		2006		% Change	
	Actual	Old	New	St. Est.	Old	New	2005	2006
1Q	0.23A	0.51A	0.51A	0.51A	0.46E	0.46E	122%	-10%
2Q	0.44A	0.48A	0.48A	0.48A	0.27E	0.27E	9%	-44%
3Q	0.47A	0.42A	0.42A	0.42A	0.26E	0.26E	-11%	-38%
4Q	0.49A	0.42E	0.42E	0.42E	0.29E	0.29E	-14%	-31%
Year	1.63A	1.83E	1.83E	1.83E	1.29E	1.29E	12%	-30%
P/E	14.2		12.7			17.9		

Market Data

Market Cap (Mil)	20160
Shares Outstanding (Mil)	840.00
Float (%)	574
Dividend Yield	N/A
Convertible	No
52 Week Range	35.26 - 22.80

Financial Summary

Revenue FY05 (Mil)	6315.0
Five-Year EPS CAGR	16.0
Return on Equity	30.00
Current BVPS	4.64
Debt To Capital (%)	30.62

Stock Overview**Stock Rating****Target Price**

New: 1-Overweight	New: \$ 31.00
Old: 1-Overweight	Old: \$ 31.00

Sector View: 1-Positive

- Over the course of this week we will be writing a series of notes highlighting four key risks facing BSX: intellectual property or patent risk, legal and legal liability risk, regulatory risk and integration risk. Each individual note will explore a different risk with today's note focusing on intellectual property risk. On the legal risk front however, it is worth noting that over the weekend the New York Times reported that the US attorney's office in Minneapolis issued a subpoena for records disclosed in a Texas lawsuit that suggest the Government is undertaking a broad investigation of GDT including the potential for Medicare fraud. This is not surprising as we already knew the Government was interested, but the potential ramifications are meaningful and must be explored as we will later this week. The purpose of these notes is to provide investors with more information to assess the risk profile of BSX as BSX's valuation and pending acquisition of GDT have created significant interest in the stock.
- Intellectual Property Risk: As is typical in medical device land, BSX is involved in a number of litigations. Given that BSX is about to become a more highly leveraged company and that some of the current patent cases involve BSX's most important pipeline products,

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PLEASE SEE ANALYST(S) CERTIFICATION(S) ON PAGE 5 AND IMPORTANT DISCLOSURES BEGINNING ON PAGE 6

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the stakes are higher than normal. To bottom line it, we believe BSX's IP risk is manageable despite our view that BSX is more likely than not to come up on the short-end on a number of key upcoming decisions including Ding. We should hear a key decision on the Ding patent sometime in the next few months. Most of the key patent cases that BSX faces today involve JNJ and include the Palmaz-Schatz litigation, the Ding litigation, the Gray litigation, the Jang litigation, the Grainger litigation and a number of others. There are even hypothetical litigations to contend with as JNJ has strongly suggested that they feel GDT and ABT may violate JNJ/Wyeth DES patents covering the "limus" family of drugs. BSX has not reserved any meaningful amount of money for currently pending IP litigation. The upcoming ruling on Ding from Judge Robinson of Delaware is the most important as a BSX victory would not only increase the probabilities that Liberte could launch without a problem, but it might also have a positive impact on the amount that BSX ultimately pays JNJ on the Palmaz litigation. If the Ding decision goes against BSX, investors would assume Liberte may never come to market, which would be a negative for investor sentiment towards BSX but it would not change our current BSX EPS estimates by more than a few pennies as we feel the market share loss relative to our current model would be less than 5 points. Liberte is a potential source of upside, but most seem to have modeled it conservatively.

- Importantly, it is our opinion that BSX faces little potential liquidity risk from these litigations as most of these law suits involve future products that have yet to truly launch in the US, which suggests little potential for damages. The Palmaz litigation could involve \$500mm-\$1bn in damages to JNJ, but that is something that investors have been aware of for a long time and we believe is manageable. The Ding ruling is critical because if BSX loses, BSX may not be able to launch its next generation DES (Liberte) in the US. Because BSX will now potentially have access to GDT's Xience stent however, the risk to BSX from not having Liberte is somewhat mitigated in our view especially considering that JNJ's pipeline remains an unknown and that JNJ Palmaz patents expired last year. We believe Judge Robinson will most likely overturn the Jury decision on Ding and hand JNJ a victory for reasons that we explain in the note, and while this will create considerable noise in the market place, our 2007 BSX EPS number of \$1.47 would decline by less than \$0.05. Liberte is scheduled to come to market late Q3 or early Q4 of this year and Xience is due out Q3:07. See the attached note for full details on all litigations.

BSX Litigation: An Overview

In the following sections, we outline the majority of outstanding patent cases between JNJ and BSX on bare metal and drug-eluting stent technology, discussing those decisions that have gone in favor of BSX and JNJ and those yet to be decided. In addition, we attempt to quantify the potential damages BSX may owe JNJ, which could total as much as \$900 mm (\$550 mm or so for Express and Liberte and \$350 mm for infringement by the NIR stent) in retro- and prospective royalties, by our calculations. However, if BSX is victorious on Ding, we believe it would swing the leverage back to BSX and any damages would likely be minimized if the two parties decide to trade IP rights (and money) in exchange for a settlement. If BSX loses on Ding, BSX's access to the Xience stent via the GDT merger would prevent any real market share damage in our view and while the economics to BSX from Xience sales are much less than from any TAXUS sales, we have taken this into account in our models.

IP Summary – What you Need To Know

Essentially all DES manufacturers have been found in violation of JNJ's Palmaz-Schatz patent and BSX is no exception. While this patent has expired, we are waiting for the damages phase to hear how much BSX will owe JNJ for sales of its Express stents before the expiration. We estimate between \$500mm and \$1bn could be owed. BSX's Liberte stent has also been found to be in violation of JNJ's Gray patent, but JNJ's Cypher stent has been found to violate BSX's Ding patent and if that ruling sticks, BSX would have a great deal of leverage over JNJ, which could limit the amount BSX has to pay JNJ on Palmaz and limit JNJ's ability to shut down Liberte. A horse trade would be likely in that situation. BSX's Ding patent describes the use of a topcoat in a DES polymer and a jury ruled late last year that JNJ's Cypher DES system violates this key patent. Cypher is the only DES system JNJ sells. In addition to planning an appeal on Ding, JNJ is asking the Judge overseeing the case to overturn the Jury verdict and throw out the decision. If the Judge overturns the Jury verdict BSX's Liberte stent would be at risk because BSX's leverage over the Gray ruling would go away. JNJ has also been found to violate the Jang patent, but BSX's right to Jang seems in doubt. The damages phase on Palmaz seems to be on hold until the Ding decision.

Outside of Ding, Jang, Gray and Palmaz, BSX is also suing JNJ in the US on the Grainger patent, which describes the use of systemic drugs delivered on a stent. The case was originally scheduled to be heard in October (by Judge Robinson), but has since been rescheduled for March of 2006. JNJ has also made some recent assertions that GDT's everolimus may infringe JNJ IP covering the use of limus compounds (JNJ uses the parent compound, Sirolimus) in DES platforms, however none of those patents have been litigated and, to our knowledge, no suits have been filed as of yet. Also worth mentioning, BSX has been victorious in Europe on IP, effectively forcing JNJ to shift manufacturing out of the Netherlands, but this transition appears to have occurred seamlessly and therefore we doubt it provides BSX any significant leverage. Also worth mentioning, BSX has agreed to pay Medinol \$750 mm in damages relating to the NIR stent – the settlement provides an end to most of the litigation risk, though there are still outstanding cases by both parties that were not included in the settlement.

In summary, BSX has won the initial rounds of litigation against JNJ on two important US patents – Ding and Jang, which cover polymer coatings for DES and bare metal stent architecture, respectively. JNJ has been victorious on the Palmaz-Schatz and Gray patents, which describe bare metal stent architecture – Express2 violates Palmaz, while Liberte violates both. Importantly, Palmaz-Schatz expired in November of 2005, but the Gray patent will be enforceable until 2016. The court has yet to decide on infringement for Liberte DES because it has yet to be launched in the US, but given that Liberte DES is, in effect, the Liberte stent, we believe there is a high probability Liberte DES (as well as Barracuda, which has the same stent architecture) will infringe Gray.

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With respect to timing, the key events we are waiting for are: 1) Judge Robinsons' decision on motions to overturn jury rulings on Ding and Jang as well as BSX motions to overturn Palmaz and Gray, with Ding being the key and JNJ having a reasonable chance of prevailing, in our opinion. No dates have been set, but final briefs were filed in October of 2005 and a ruling could come at any point; 2) JNJ is awaiting reinstatement of a \$342 mm damages ruling for BSX's infringement with the NIR stent; 3) following the motions to overturn, all these cases will enter damages phases, with monetary awards to be decided and 4) all these decisions will be appealed, and importantly, BSX has not reserved for any of the potential damages for each of these cases.

BSX Wins: The Ding and Jang Patents

On July 2nd 2005, a jury handed down a surprising victory to BSX by ruling that JNJ's Cypher drug-eluting stent, among others, infringes BSX's Ding and Jang patents; the jury also ruled that the patents were valid. Ding describes a polymer with a top coat while Jang covers specific stent geometry. Please see Figures 1 and 2 below for specific patent details and wording.

Figure 1: BSX Patent Wins

Key Patents Under Litigation						
Patent Assignee	Patent No.	Date of Filing	Date of Issue	Inventor	Title	Abstract
BSX	6,120,536	6/13/1996	9/19/2000	Ding	Medical devices with long-term non-thrombogenic coatings	A coating and method for implantable open lattice metallic stent prostheses are disclosed. The coating includes a relatively thin layer of biostable elastomeric material containing an amount of biologically active material, particularly heparin, dispersed in the coating in combination with a non-thrombogenic surface. In one embodiment, the surface is provided with sites of high electronegativity species by coating with fluorosilicone which aid in controlling elution, particularly the initial release rate, and reduced thrombogenic activity. Other non-thrombogenic outer layers for heparin such as covalently bound polyethylene glycol (PEG) are also disclosed.
BSX	5,922,021	4/25/1997	7/13/1999	Jang	Intravascular stent	A stent in a non-expanded state has a first expansion strut pair consisting of a first expansion strut positioned adjacent to a second expansion strut and a joining strut which couples the first and second expansion struts at a distal end of the first expansion strut pair. A plurality of the first expansion strut pair form a first expansion column. A second expansion strut pair consists of a first expansion strut positioned adjacent to a second expansion strut and a joining strut couples the first and second expansion struts at a proximal end of the second expansion strut pair. A plurality of the second expansion strut pair form a second expansion column. A first connecting strut includes a first connecting strut proximal section, a first connecting strut distal section and a first connecting strut intermediate section. The first connecting strut proximal section is coupled to the distal end of the first expansion strut pair in the first expansion column and the first connecting strut distal section is coupled to the proximal end of the second expansion strut pair of the second expansion column. A plurality of the first connecting struts form a first connecting strut column that couples the first expansion column to the second expansion column. A length of the first connecting strut proximal section is equal to a length of the first connecting strut distal section, and a length of the first connecting strut intermediate section is greater than the length of the first connecting strut proximal and distal sections.

Source: US Patent Office

Figure 2: Key Ding Patent Claims

Key Ding Patent Claims Under Litigation (BSX Patent No. 6,120,536)	
Claim No.	Description
1	A medical device having at least a portion which is implantable into the body of a patient, wherein at least a part of the device portion is metallic and at least part of the metallic device portion is covered with a coating for release of at least one biologically active material, wherein said coating comprises an undercoat comprising a hydrophobic elastomeric material incorporating an amount of biologically active material therein for timed release therefrom, and wherein said coating further comprises a topcoat which at least partially covers the undercoat, said topcoat comprising a biostable, non-thrombogenic material which provides long term non-thrombogenicity to the device portion during and after release of the biologically active material, and wherein said topcoat is substantially free of an elutable material.
6	The device of claim 1 wherein the medical device is an expandable stent.
8	The device of claim 6 wherein the stent comprises a tubular body having open ends and an open lattice sidewall structure and wherein the coating conforms to said sidewall structure in a manner that preserves said open lattice.

Source: U.S. Patent Office web site

JNJ's Prospects for Appeal on Ding

Following the jury's decision on Ding, JNJ filed a motion with Judge Robinson to vacate the ruling based both on the narrow definition of important terms in claim 1 (see Figure 2 above), particularly the meaning of elastomeric, as well as the existence of prior art. Though the jury found that Ding was valid and JNJ did infringe, we continue to believe JNJ has several valid arguments that could serve the basis for a strong appeal and while there has been precedent for a Judge to overrule a decision from the bench, the likelihood of this occurring seems low. Specifically, in our review of the patent and the comments/rulings by Judge Robinson prior to the decision, we believe JNJ will again

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argue in its appeal that it does not infringe Ding, citing, among other things, the very specific definition of elastomeric coatings. In the Markman hearings (claims construction), an "elastomeric" material was defined by Judge Robinson as "a material able to stretch or expand without breaking, and to return to its original dimensions." JNJ has previously described Cypher as having an elastomeric coating, however during the trial, the company presented evidence which Judge Robinson cited in her decision that the coating does indeed crack when the stent is expanded — Judge Robinson, in her decision, specifically stated uncertainty as to whether, by the letter of the law, such a narrow definition would be inclusive of JNJ's stent. Despite the Jury's ruling, JNJ may continue to use this argument in its appeal. With respect to prior art, several patents describing polymers on stents do exist (Fox, Domb, Myler), however with BSX having now received two affirmations of validity (from the patent office and Friday's jury decision), the probability the patent is found to be invalid would seem low.

Other Litigation: BSX's Grainger Patent

Finally, March of 2006, JNJ and BSX will go back to trial once again to litigate the next IP case over BSX's Grainger patent (6,251,290), which describes the systemic (oral administration) and site-specific (on a stent) usage of therapeutic compounds (tamoxifen derivatives) to treat cardiovascular disease. No updates have been given and timing of a ruling is unclear, other than to say Judge Robinson will likely rule on the outstanding cases (Ding, Gray, Palmaz, etc) prior to rendering a decision on Grainger.

JNJ's Wins: Palmaz-Schatz and Gray and the NIR stent

On June 21st, 2005 a U.S. jury in the federal court of Delaware found that BSX's Express2 and Liberte bare metal stents and Taxus drug-eluting stent infringe JNJ's Palmaz-Schatz patent (expired in November 2005) and that Liberte also infringes JNJ's Gray patent (expires in 2016). The finding of infringement on the Palmaz-Schatz patent is not unexpected and the damages phase of the trial will be set after Judge Robinson rules on motions to overturn the jury decisions on Ding, Jang, Palmaz and Gray. The ruling on the Gray patent gives JNJ some meaningful leverage as it could allow JNJ to seek an injunction on BSX's Liberte DES platform or at least seek a royalty on Liberte DES sales when that device is approved around mid-2006, although BSX would be free to revert to the GDT Xience V stent.

In addition, on March 24, 2005 JNJ was victorious in a multi-year battle against BSX involving the NIR stent. JNJ originally won in 2000, but the court set aside the decision in 2002 and sent it back to trial which finally decided in JNJ's favor in March. JNJ is seeking reinstatement of the original \$324 mm damages awarded (plus interest). This decision could come any day.

Damages on Palmaz and Ding: What could BSX Have to Pay?

Assuming BSX loses on Ding and has little to no leverage in settlement/cross-licensing negotiations, we calculate that BSX could owe JNJ approximately \$900 mm, comprised of \$342 mm (plus interest) on NIR, and \$550 mm for Express and Liberte. The latter could be reduced (perhaps to \$200-300 mm) if BSX launches Xience in 2007 and continues selling Express2 (and not Liberte) which violates only the expired Palmaz patent, not Gray. Figure 3 below lays out the calculation damages. Our calculation involves applying a 15% royalty rate (an amount equivalent to that paid by GDT to JNJ in a similar ruling) to both Taxus and Express 2/Liberte sales from launch. On Taxus damages, we apply the royalty to only the bare metal portion of the stent as Gray and Palmaz only cover bare metal stent architecture. Of note, JNJ could seek treble damages award for willful infringement on Palmaz and Gray, which could bring the award well north of \$1 billion, but the hurdle for such an outcome is high, in our opinion.

Figure 3: BSX Potential Payments to JNJ

BSX Payment to JNJ								
Cumulative BMS + DES Sales	2002A	2003A	2004A	2005A	2006E	2007E	2008E	Total
US Revenues (\$MM)								
Express/Liberte BMS	\$90	\$209	\$60	\$27	\$16	\$15	\$15	\$432
TAXUS/Liberte DES	0	0	1,571	1,762	1,660	1,933	1,125	8,051
Total	\$90	\$209	\$1,632	\$1,789	\$1,676	\$1,948	\$1,140	\$8,483
ASPs (\$)								
Express/Liberte BMS	\$1,050	\$915	\$910	\$910	\$850	\$850	\$850	\$931
TAXUS/Liberte DES	\$0	\$0	\$2,580	\$2,450	\$2,260	\$2,050	\$1,900	\$2,238
Unit Sales								
Express/Liberte BMS	85,519	227,869	66,264	29,670	18,824	17,647	17,647	463,440
TAXUS/Liberte DES	0	0	609,070	719,184	734,513	842,927	592,105	3,597,799
Total	85,519	227,869	675,334	748,854	753,337	960,574	609,752	4,061,238
Adjusted Revenues (\$MM)								
Express/Liberte BMS	\$90	\$209	\$60	\$27	\$16	\$15	\$15	\$432
TAXUS/Liberte DES	0	0	554	654	624	801	503	3,138
Total	\$90	\$209	\$615	\$681	\$640	\$816	\$518	\$3,569
Royalty Assumption								
Royalties on Express	\$14	\$32	\$95	\$106	\$0	\$0	\$0	\$247.0
Royalties on Liberte	\$0	\$0	\$0	\$0	\$99	\$126	\$80	\$305.9
Total Royalties Due (\$MM)	\$13.9	\$32.3	\$95.2	\$105.6	\$99.2	\$126.5	\$80.3	\$552.9

Source: Company data; Lehman estimates

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Analyst Certification:

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Other Team Members:

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Company Description:

Boston Scientific is a global medical technology company focused on less invasive medicine, specifically interventional cardiology, radiology, neurology, and urology products.

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Important Disclosures:

Boston Scientific (BSX)

\$ 23.15 (26-Jan-2006)

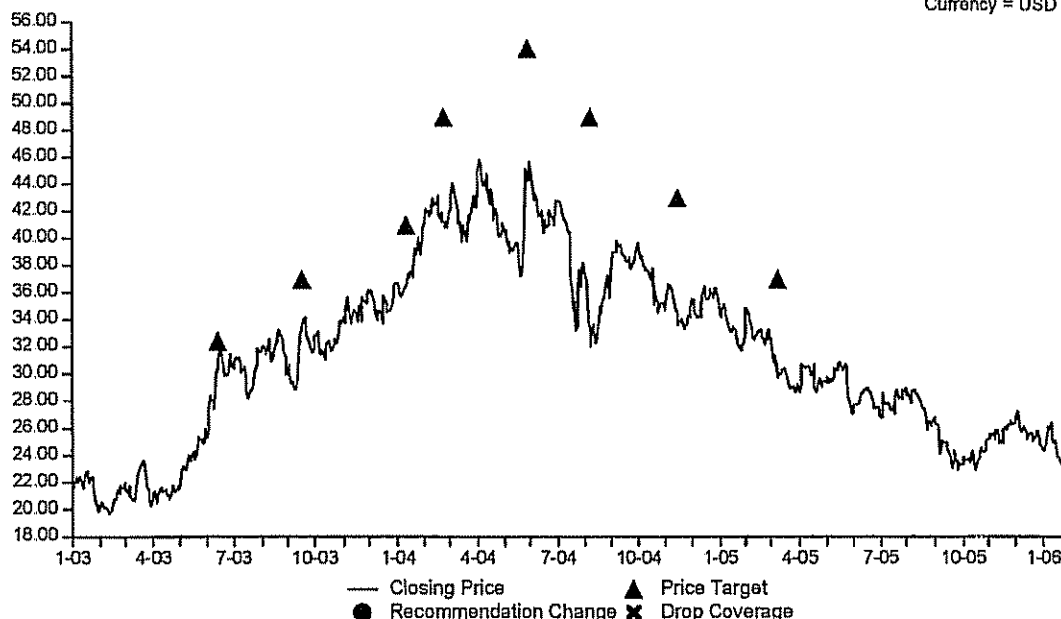
1-Overweight / 1-Positive

Rating and Price Target Chart:

BOSTON SCIENTIFIC

As of 24-Jan-2006

Currency = USD



Source: FactSet

Currency=\$

Date	Closing Price	Rating	Price Target
09-Mar-05	29.75		37.00
15-Nov-04	34.60		43.00
06-Aug-04	33.21		49.00
28-May-04	44.30		54.00
24-Feb-04	41.27		49.00

Date	Closing Price	Rating	Price Target
12-Jan-04	36.40		41.00
16-Sep-03	33.25		37.00
12-Jun-03	30.43		32.50

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Valuation Methodology: Our \$31 price target is derived from a 18 5x multiple off our 2008 cash EPS estimate of \$1.68.

Risks Which May Impede the Achievement of the Price Target: Exposure to emerging drug-eluting stent market. Exposure to interventional cardiology market. Competition from other drug-eluting stent players. Acquisition integration. Risk from pending litigation.

Other Material Conflicts: One of the analysts on the coverage team (or a member of his or her household) owns common stock and options in the common stock of Boston Scientific.

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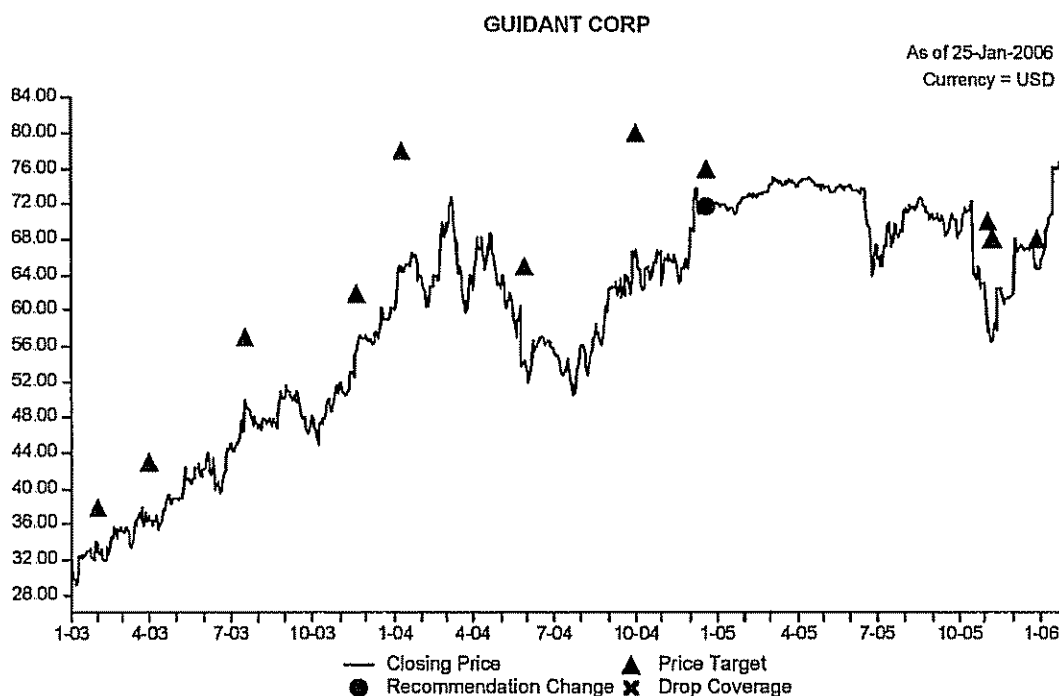
Important Disclosures Continued:

Guidant Corp (GDT)

\$ 75.26 (26-Jan-2006)

2-Equal weight / 1-Positive

Rating and Price Target Chart:



Source: FactSet

Currency=\$

Date	Closing Price	Rating	Price Target
29-Dec-05	64.85		68.00
10-Nov-05	57.75		68.00
08-Nov-05	56.53		68.00
03-Nov-05	57.57		70.00
21-Dec-04	71.70		76.00
21-Dec-04	71.70	2-Equal weight	
01-Oct-04	66.76		80.00

Date	Closing Price	Rating	Price Target
28-May-04	54.34		65.00
12-Jan-04	64.96		78.00
20-Nov-03	55.35		62.00
17-Jul-03	49.96		57.00
02-Apr-03	36.48		43.00
31-Jan-03	33.62		38.00

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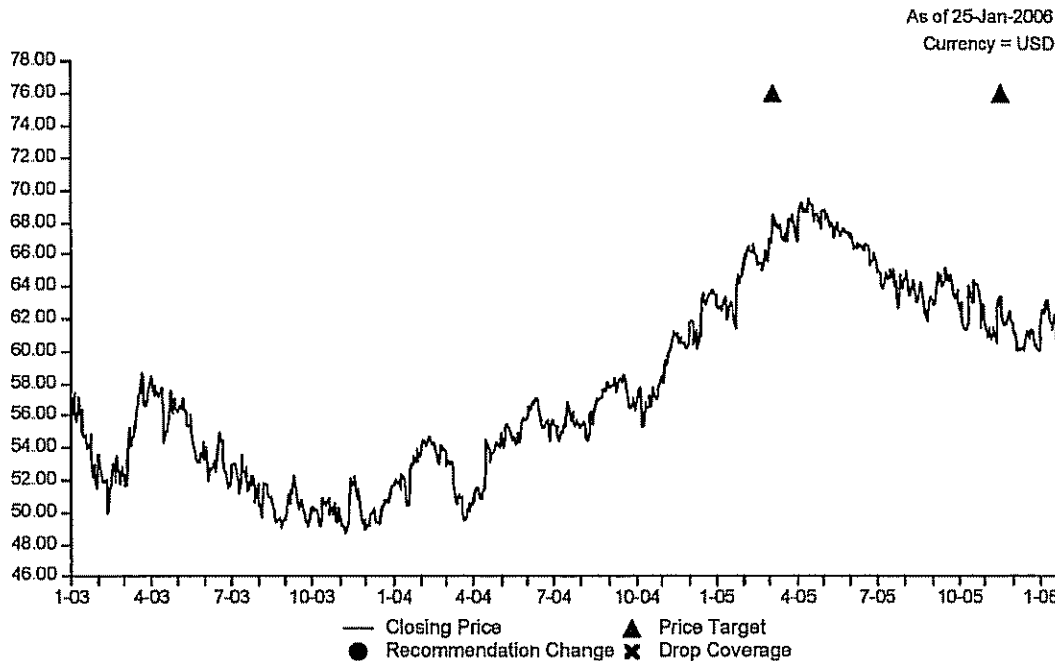
Johnson & Johnson (JNJ)

\$ 58.64 (26-Jan-2006)

1-Overweight / 1-Positive

Rating and Price Target Chart:

JOHNSON & JOHNSON



Source: FactSet

Currency=\$

Date	Closing Price	Rating	Price Target
17-Nov-05	63.34		76.00

Date	Closing Price	Rating	Price Target
07-Mar-05	68.44		76.00

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Company Name	Ticker	Price (26-Jan-2006)	Stock / Sector Rating
Boston Scientific	BSX	\$ 23.15	1-Overweight / 1-Positive
Related Stocks	Ticker	Price (26-Jan-2006)	Stock / Sector Rating
Guidant Corp	GDT	\$ 75.26	2-Equal weight / 1-Positive
Johnson & Johnson	JNJ	\$ 58.64	1-Overweight / 1-Positive

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Bausch & Lomb (BOL)	Biomet, Inc (BMET)
Boston Scientific (BSX)	Conor Medsystems (CONR)
DJ Orthopedics (DJO)	Greatbatch Inc. (GB)
Guidant Corp (GDT)	Johnson & Johnson (JNJ)
Medtronic Inc (MDT)	Novoste Corp (NOVTD)
Nuvasive Inc (NUVA)	St. Jude Medical (STJ)
Stryker Corp (SYK)	Syneron Medical (ELOS)
Thoratec Corp (THOR)	Wright Medical Group (WMGI)
Zimmer Holdings (ZMH)	

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2-Equal weight - The stock is expected to perform in line with the unweighted expected total return of the sector coverage universe over a 12-month investment horizon.

3-Underweight - The stock is expected to underperform the unweighted expected total return of the sector coverage universe over a 12-month investment horizon.

RS-Rating Suspended - The rating and target price have been suspended temporarily to comply with applicable regulations and/or firm policies in certain circumstances including when Lehman Brothers is acting in an advisory capacity in a merger or strategic transaction involving the company.

Sector View

1-Positive - sector coverage universe fundamentals/valuations are improving

2-Neutral - sector coverage universe fundamentals/valuations are steady, neither improving nor deteriorating

3-Negative - sector coverage universe fundamentals/valuations are deteriorating.

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Exhibit K

Link to full report including important disclosures*
http://rschl.ml.com/9093/24013/ds/2768242_.PDF

New JNJ stent manufacturing now coming on line
 The first manufacturing line for Johnson & Johnson's (JNJ;A-1-7;\$59.29) Cypher drug eluting stent (DES) is scheduled to come on line this month with one line per month to be added over the next 3 months. With the new Cypher capacity, JNJ expects to realize share gains over the next few quarters. Of the ~1,600 U.S. interventional cardiology labs, JNJ estimates it has a presence in ~800 of which 500 get preferential allocation of Cypher. In those 500 targeted accounts, JNJ pegs its DES market share at upwards of 60%.

JNJ-GDT co-promotion agreement could remain in place
 The pending sale of Guidant's (GDT;RSTR;\$77.55) Vascular Intervention franchise to Abbott (ABT;B-1-7;\$45.16) in conjunction with Boston Scientific's (BSX;B-2-9; \$22.95) pending purchase of Guidant does not void the existing JNJ-GDT co-promotion agreement for Cypher. JNJ has indicated that it will review the arrangement post closing of the deal, which could result in a cessation of the arrangement or a continuation pending the approval of Guidant's Xience DES in the U.S. (late 2007/ early 2008).

New DES products expected in 2007 from JNJ
 In early '07, JNJ expects to launch the Cypher Select in Europe with an enhanced delivery system to be followed with Cypher in 2.25mm and 4.00mm diameters. Next up in the U.S. is the Cypher Nxt, which is Cypher on GDT's Vision delivery system. Further back in the queue is: 1) Project Python, a new stent/delivery system (U.S.) , 2) Cypher Neo, a cobalt chrome DES based on a new stent design/delivery system (WW) and 3) Firefox, a cobalt chrome DES based on a new stent/delivery system which is characterized as a "workhorse" stent that will also be targeted at small vessels. And as part of the JNJ-GDT cross-licensing agreement, JNJ has rights to GDT's bioabsorbable DES (enrollment in the ABSORB trial evaluating GDT's bioabsorbable stent is underway).

More legal wrangling from JNJ possible
 JNJ has two patents (Wright and Falotico), which appear to relate to the elution characteristics of "olimus" compounds; JNJ's Cypher DES uses sirolimus, a member of the olimus family of drugs; other olimus drugs include Guidant's everolimus and Abbott/Medtronic's zotarolimus (ABT-578). The European launch of Guidant's Xience DES, which the company has targeted for Q2:06, could trigger possible legal activity since we understand U.S. patent law prohibits domestic manufacture of a product for sale outside the U.S. if there's been infringement of intellectual property.

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Exhibit L

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The International Herald Tribune

January 23, 2006 Monday

SECTION: FINANCE; Pg. 12

LENGTH: 750 words

HEADLINE: J&J works to discredit rival offer for Guidant;
MARKETPLACE by Bloomberg

BYLINE: Avram Goldstein

DATELINE: WASHINGTON

BODY:

Johnson & Johnson, facing a deadline on Tuesday for raising its bid to acquire the cardiac device maker Guidant, is trying to sow doubts among investors about Boston Scientific's rival offer, according to analysts.

Johnson & Johnson, the world's biggest maker of medical devices, and its advisers told securities analysts last week that Boston Scientific would borrow too much for the deal, according to analysts at Prudential Equity Group and A.G. Edwards.

J&J also said Boston Scientific had been making unrealistic financial projections to justify its \$27 billion offer to buy Guidant, almost \$3 billion more than Johnson & Johnson's.

"J&J is communicating to the Street that Boston Scientific's \$80-a-share offer for Guidant is fraught with uncertainty," Lawrence Biegelsen, an analyst with Prudential in New York, said in a note to clients sent on Friday. The campaign, he said, suggests "that J&J is still very interested in acquiring Guidant and that J&J will likely increase its offer at least one more time."

The Guidant transaction would be the biggest purchase of a medical device company. Guidant, the second-largest maker of implantable defibrillators and pacemakers, behind Medtronic, is developing a cardiac stent that would pose a competitive threat to rival products of J&J and Boston Scientific, the world's biggest maker of heart stents, tiny metal sleeves used to clear artery blockages.

A spokesman for J&J, Jeffrey Leebaw, and for Guidant, Steven Tragash, declined to comment.

J&J shares fell \$1.37, or 2.2 percent, to close last week at \$60.80 in New York Stock Exchange composite trading. Guidant dropped 17 cents, to \$75.95. Boston Scientific declined 36 cents, or 1.5 percent, to close at \$23.59.

Guidant said Tuesday that Boston Scientific's offer of about \$27 billion, or \$80 a share, of which \$42 would be in cash and \$38 in stock, was "superior" to J&J's bid of \$24.2 billion, or \$71 a share, consisting of \$40.52 in cash and the rest in J&J shares.

Johnson & Johnson's campaign consists of telling analysts and shareholders that Boston Scientific is in over its

J&J works to discredit rival offer for Guidant; MARKETPLACE by Bloom

head and is tempting patent litigation that may undercut Boston Scientific's plans.

"They're trying to tell all of us that there are patents out there that they have that they feel can stop Boston Scientific," said Jan David Wald, an analyst with A.G. Edwards. Wald said he had been called by a Johnson & Johnson employee, whom he declined to name.

Johnson & Johnson told analysts it was considering filing patent infringement lawsuits over stent drug coatings to keep Boston Scientific and its bidding partner, Abbott Laboratories, from profiting from the new Guidant devices, according to Biegelsen of Prudential.

Drug coatings on stents are designed to keep tissue growth from clogging blood vessels again.

Abbott agreed to contribute \$6.4 billion to the Boston Scientific bid and acquire Guidant's vascular business including the new cardiac stent.

Abbott shares lost \$1.19, or 2.9 percent, on Friday to close the week at \$40.35.

Patent infringement lawsuits over stent drug coatings have "no bearing on our proposed acquisition of Guidant," a spokesman for Boston Scientific, Paul Donovan, said. "Unfortunately, threats of legal action are commonplace in our industry."

Boston Scientific and J&J have been fighting in court for years over patent-infringement cases related to stent design. At the moment, the two companies are alone in the U.S. stent market, with Boston Scientific holding a 55 percent share.

Abbott, Guidant and Medtronic are all developing competing products coated with drugs similar to the one that Johnson & Johnson's stent uses.

The potential for Johnson & Johnson to prevent Abbott and Boston Scientific from marketing Guidant's next-generation heart stent "could give the Guidant board pause for approving a Boston Scientific-Guidant merger," Biegelsen said. "J&J claims that two of its patents may be infringed if a company tries to launch a drug-eluting stent coated with" Abbott's zotarolimus and Guidant's everolimus, he wrote.

After the Guidant board declared Boston Scientific's bid superior, Johnson & Johnson issued a statement calling the proposal a "highly dilutive and leveraged transaction based on extremely aggressive business projections."

The statement said the Boston Scientific bid "will not provide \$80 per share in value to Guidant shareholders."

Boston Scientific initially bid \$25 billion on Jan. 8, a month after declaring its intention to make an offer.

LOAD-DATE: January 23, 2006

Exhibit M

SUITORS TAKE GUIDANT FIGHT TO THE STREET The Boston Globe January 20, 2006 Friday

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The Boston Globe

January 20, 2006 Friday
THIRD EDITION

SECTION: BUSINESS; Pg. C1

LENGTH: 721 words

HEADLINE: SUITORS TAKE GUIDANT FIGHT TO THE STREET

BYLINE: BY STEPHEN HEUSER, GLOBE STAFF

BODY:

With the clock ticking down for Johnson & Johnson to answer Boston Scientific's \$27 billion bid for Guidant Corp., the two rivals are trying to torpedo each other's bids with Wall Street analysts and major stockholders.

Three days ago Guidant declared Boston Scientific's new offer superior, giving the Natick device maker the upper hand for the first time in a six-week bidding war. Under terms of Guidant's existing deal with Johnson & Johnson, the company has until Tuesday to boost its offer or lose Guidant.

As the day approaches, Johnson & Johnson has been raising questions about the solidity of Boston Scientific stock and the likelihood the much smaller company can actually close the deal, said two analysts who have been contacted by the firm.

Boston Scientific, to support its bid, released a set of slides on Wednesday showing a crisp month-by-month march to a completed merger and outlining plans to exceed Wall Street's earnings estimates.

"It's behind closed doors right now," said Thomas Gunderson, a medical device analyst for Piper Jaffray, of the bidding war for Guidant. "It's like watching a tennis match, but the ball has to pass through this 20-foot blind spot before the audience gets to see how the ball comes out the other side, if it comes at all."

Gunderson said he had not been contacted by Johnson & Johnson, but had a conversation with Boston Scientific earlier this week.

After more than a month of back-and-forth public statements, filings, and conference calls, the intense lobbying by both companies this week underscores their delicate positions in the bidding war over Guidant.

When Guidant's board of directors picked Boston Scientific's offer on Tuesday, Johnson & Johnson found itself out in the cold for the first time since it signed a deal to buy Guidant more than a year ago, and now must decide whether to re-enter the contest.

"I suspect that they're trying to determine what a winning bid is, and secondarily do they want to go that

high," said Robert Faulkner, an analyst for JMP Securities.

With a reputation for fiscal caution, Johnson & Johnson could be hesitant to make any bid over \$76 a share, the price it offered for Guidant in December 2004, before Guidant suffered a series of product recalls that pushed its value down.

A key concern for Boston Scientific, on the other hand, is the price of its own stock. Its \$80 bid comprises \$42 in cash and \$38 in Boston Scientific stock, but because of a "collar" provision in the offer, the value of that bid will drop sharply if Boston Scientific stock slides below \$22.62 a share. Even if it gets close to that number, many investors' models will begin assigning a lower value to the bid, and Johnson & Johnson could woo Guidant back with a lower bid.

Boston Scientific stock dropped by more than \$1 on Tuesday when it made its \$80-per-share offer, but has been largely steady since then at just under \$24 a share. It closed at \$23.95 last night, up 1 cent on the day.

Johnson & Johnson launched its first salvo on Tuesday night, after Guidant gave the nod to Boston Scientific. In an unusually terse statement, the New Jersey healthcare giant attacked the fundamental value of the Boston-Guidant deal, calling it "based on extremely aggressive business projections."

Since then, the company has raised similar questions in phone conversations with analysts who value medical device companies. It has also raised the prospect that it could use patents and existing ties to Guidant to derail or complicate Boston Scientific's offer, said Matthew Dodds, an analyst for Citigroup who is skeptical about Guidant's value to both companies.

Johnson & Johnson is "strongly suggesting" that it could tie up the deal past Boston's estimated completion date of March 31, he said, and questioned the business estimates it is based on.

"They're talking about the excessiveness of the Boston Scientific deal, how they don't believe the numbers can work," he said.

Contacted for this story, Johnson & Johnson would not discuss details of its conversations with investors.

A Boston Scientific spokesman said the deal at this point would come down to the numbers.

"We're at \$80, and J&J is at \$71," he said. "Guidant has declared us superior, and we're working very hard to close this deal as soon as possible."

Stephen Heuser can be reached at sheuser@globe.com.

GRAPHIC: PHOTO

LOAD-DATE: January 20, 2006

Exhibit N

CHICAGO BUSINESS
— POWERED BY CRAIN'S —

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Abbott stock falls on concerns over success of Guidant bid

By Paul Merrion
Jan. 20, 2006

(Crain's) — Abbott Laboratories stock took a tumble today after a research analyst raised the possibility that Abbott and another company, Boston Scientific Corp., may not win the bidding for Guidant Corp.

The analyst, Prudential Equity Group, LLC's Larry Biegelsen, reported that Guidant's board could balk at Boston Scientific and Abbott's joint bid because Johnson & Johnson, a competing bidder for Guidant, claims its patents would be violated if Abbott markets its own drug-eluting stents or those made by Guidant. That could give Guidant's board pause in approving Boston Scientific's bid, Mr. Biegelsen wrote.

Abbott's shares closed down \$1.19, or 2.9%, to \$40.35 on Friday, capping two weeks of declines that wiped out a 3.7% gain Jan. 9, when investors bid up Abbott's stock on enthusiasm for the potential deal.

Since the bid was announced, Abbott has raised its offer to \$4.1 billion and agreed to loan \$900 million to Boston Scientific, which would acquire the rest of Guidant. Abbott also is agreeing to buy \$1.4 billion worth of Boston Scientific's stock to help that company outbid Johnson & Johnson in the takeover battle for Guidant.

Abbott was not available for comment.

"We believe this issue (J&J's patent claim) has no bearing on our proposed acquisition of Guidant," says a spokesman for Boston Scientific. "Unfortunately, threats of legal action are commonplace in our industry."

Abbott CEO Miles D. White is trying to diversify his product line so it isn't so reliant on drug sales. Abbott sees the Guidant deal as a rare opportunity to quickly become a big player in the market for stents, tiny cylinders used to prop open clogged arteries to the heart and brain. Abbott is developing its own products but would gain those already sold by Indianapolis-based Guidant, in addition to research and a salesforce.

But there are risks involved in getting into a business in which Abbott will play catch-up.

"They're increasing the price and increasing their exposure" to risk, says Ignatius Smetek, president and chief investment officer of Abbott shareholder Arcataur Capital Management LLC in Milwaukee.

For instance, North Chicago-based Abbott would acquire a drug-coated heart stent Guidant is developing. Drug-coated stents are supposed to be effective at keeping arteries from reclogging after heart procedures, and the market for these products may reach \$8 billion by 2011, Boston Scientific estimates.

But Abbott, which hopes to have a drug-coated stent on the market by 2008, would enter several years behind New Jersey-based Johnson & Johnson and Massachusetts's Boston Scientific, which already have products on

the market. Medtronic Inc. also is developing a drug-coated stent.

"It will be difficult to significantly penetrate that market," says Mark Morasch, a vascular surgeon and assistant professor at Northwestern University's Feinberg School of Medicine.

Exhibit O

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Reuters News

January 20, 2006 Friday 8:35 PM GMT

LENGTH: 411 words

HEADLINE: UPDATE 2-Abbott, Boston shares off on J&J patent threat

DATELINE: January 21, 2006

BODY:

(Adds J&J shares)

CHICAGO, Jan 20 (Reuters) - Shares of Abbott Laboratories Inc. and Boston Scientific Corp. fell on Friday on concerns that Johnson & Johnson <J&J.N> could have patents that might put Boston Scientific's bid for heart device maker Guidant Corp. at risk.

In a research note on Friday, Prudential analyst Larry Biegelsen said J&J claims that two of its patents may be infringed if a company tries to launch a drug-eluting stent coated with a derivative of rapamycin. The drug compound is used to enhance the performance of the stents, or tiny wiremesh tubes.

J&J's Cypher stent is coated with such a compound. So are the experimental stents under development by Abbott and Guidant.

Boston Scientific and Johnson & Johnson are locked in a bidding war over control of Guidant, a maker of heart devices to treat irregular heartbeats and clogged heart arteries.

Guidant's board has said Boston Scientific's offer of \$80 per share in cash and stock is superior to a \$73 bid by J&J.

Boston Scientific's shares edged down 36 cents, or 1.5 percent, to close at \$23.59, while Abbott slid \$1.19, or 2.86 percent, at \$40.35 amid a broadly weaker market. Shares of J&J also fell \$1.37, or 2.2 percent, to \$60.80.

"The potential for J&J to prevent Abbott Laboratories and Boston Scientific from marketing (Guidant's Xience-V stent) could give the Guidant board pause," Biegelsen wrote.

"We believe this issue has no bearing on our proposed acquisition of Guidant. Unfortunately, threats of legal action are commonplace in our industry," said Paul Donovan, a spokesman for Boston Scientific.

UPDATE 2-Abbott, Boston shares off on J&J patent threat Reuters News

Abbott spokesman Jonathon Hamilton said the company was undeterred by the report. "We are confident we have freedom to operate," Hamilton said of Abbott's stent. "With respect to Guidant's product, it would be inappropriate for us to comment," he said.

J&J representatives declined to comment.

Many analysts expressed skepticism, saying the concerns over intellectual property were overblown.

One analyst, who asked not to be named, said J&J management was making rounds on Wall Street, trying to fan fears about the Boston Scientific bid.

The analyst said J&J was arguing that Boston Scientific's bid was breaking its bank, that its assumptions on Guidant's cardiac rhythm management were too aggressive and that there was intellectual property infringement that would limit potential of important products. (Additional reporting by Lewis Krauskopf in New York)

NOTES: HEALTH-ABBOTT (UPDATE 2)|LANGEN|ABN|E|RBN|U|M|D|RNP|DNP;
PUBLISHER: Reuters Ltd.

LOAD-DATE: January 21, 2006

Exhibit P

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Medical Device Week

January 24, 2006

ACC-NO: 142590071

LENGTH: 1006 words

HEADLINE: J&J offer rumors persist as Guidant has more ICD issues.

BODY:

J&J offer rumors persist as Guidant has more ICD issues

By HOLLAND JOHNSON

Medical Device Daily Associate Managing Editor

As the bidding war for Guidant (Indianapolis) continued to play itself out as the week began, several new factors were added to an already much-too-complex equation.

Guidant, which already has reported a slew of problems with its pacemakers last year, on Monday reported a new problem with some of its older devices. Additionally, rumors began to fly that Johnson & Johnson (J&J; New Brunswick, New Jersey), the original suitor in the escalating bid to acquire Guidant, was poised to make a higher offer for the company.

Guidant said it had identified a second batch of older-model pacemakers that are at risk of malfunction due to a problem with a sealing component. The company recommended physicians reassess their patients due to the discovery of additional devices with the potential defect.

Guidant, which said there have been 145 incidents of malfunction to date related to the seal problem, estimated 16,000 of the affected devices remain implanted in patients worldwide.

This new leak disclosure adds to a previous physician notification made this past July (Medical Device Daily, July 19, 2005).

At the time of the first notification, the company said that as of July 11 it had identified 69 devices that may have exhibited this failure, from about 78,000 devices distributed with this component, with about 28,000 devices still implanted worldwide.

It said that no failures were reported for the first 44 months of device use but that "the likelihood of occurrence increases with implant time." Of the 28,000 devices identified and implanted worldwide, 18,000 of them remain in service in the U.S., with an average implant age of 69 months.

As of Jan. 9, a total of five reported incidents out of the second identified patient population of 54,000 represented a

J&J offer rumors persist as Guidant has more ICD issues. Medical Dev

rate of occurrence of 0.009%. Guidant said it has confirmed hermetic seal degradation in two of the five reports. It is estimated that 19,300 devices in this second population remain implanted worldwide.

At the time devices in the second population were assembled, the company said hermetic sealing components susceptible to gradual degradation were mistakenly mixed with a much larger group of non-susceptible components.

The devices in this latest notification were manufactured between Oct. 19, 1998, and Dec. 5, 2000.

Guidant's warranty supplement program, subject to certain conditions, provides a no-cost replacement device and up to \$2,500 in unreimbursed medical expenses. The program is available through June 30 and is applicable to both patient populations.

Apparently neither this latest news, nor the documents un-sealed in a Texas court last week that showed that Guidant executives had debated whether to tell doctors about possible heart device malfunctions six months before the problems were publicly disclosed, has deterred J&J from making a possible new increased offer for the embattled, but apparently Teflon-coated company.

Rumors began circulating on Monday that J&J would raise its offer, possibly during its quarterly earnings report today, to somewhere in the neighborhood of \$77 to \$78 a share - still significantly below rival suitor Boston Scientific's (Natick, Massachusetts) most recent \$80 a share bid - but higher than its own initial December 2004 \$76-a-share offer.

Fueling this speculation were rumors, some of which apparently were planted by J&J personnel as part of an organized campaign to undermine the Boston Scientific offer in the minds of analysts, that two of its patents may be infringed if an unnamed company tries to launch a drug-eluting stent coated with a derivative of rapamycin.

J&J's Cypher stent is coated with that compound, as are the experimental stents under development by Guidant and its potential partner in the bidding war for Guidant, Abbott Laboratories (Abbott Park, Illinois). Abbott agreed to contribute \$6.4 billion to the Boston Scientific bid and acquire Guidant's vascular business including the new cardiac stent.

Larry Biegelsen, an analyst with Prudential (New York), wrote in a research report that "this potential for J&J to prevent Abbott Laboratories and Boston Scientific from marketing [Guidant's] Xience-V DES, could give Guidant's board pause approving a Boston Scientific-Guidant merger."

While Biegelsen said a \$78-a-share offer was likely, he noted that J&J, with much larger pockets than Boston Scientific, could go as high as \$90 a share for Guidant "before an acquisition of St. Jude Medical [St. Paul, Minnesota; another significant player in the cardiac rhythm management space] is more attractive."

"They're trying to tell all of us that there are patents out there that they have that they feel can stop Boston Scientific," said Jan Wald, an analyst with A.G. Edwards (Boston), in a telephone interview with Bloomberg. Wald said he was called by a J&J employee he declined to name.

As part of its recent campaign, J&J also has argued that Boston Scientific's bid was breaking its bank and that its assumptions concerning Guidant's cardiac rhythm management were too aggressive.

While Guidant's board remained silent, Guidant's suitors disputed the rumors floating around Wall Street.

"We believe this issue has no bearing on our proposed acquisition of Guidant. Unfortunately, threats of legal action are commonplace in our industry," Paul Donovan, a spokesman for Boston Scientific, said in a statement.

Abbott spokesman Jonathon Hamilton said the company was undeterred by the report. "We are confident we have freedom to operate," Hamilton said of Abbott's stent. "With respect to Guidant's product, it would be inappropriate for us to comment."

Page 3

J&J offer rumors persist as Guidant has more ICD issues. Medical Dev

Guidant said last week that Boston Scientific's offer of \$80 a share - \$42 in cash and \$38 in stock - is "superior" to J&J's current bid of \$24.2 billion, or \$71 a share, consisting of \$40.52 in cash plus 0.493 of a J&J share for each Guidant share held (MDD, Jan. 18, 2006). J&J had until today to make a counteroffer.

SOURCE-Medical Device Daily

LOAD-DATE: March 1, 2006

ABT 009620

Exhibit Q

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THE WALL STREET JOURNAL.

The Wall Street Journal

January 26, 2006 Thursday

SECTION: Pg. A1

LENGTH: 1960 words

HEADLINE: Boston Scientific Faces Pivotal Test After Victory in Fight for Guidant

BYLINE: By Thomas M. Burton, Sylvia Pagan Westphal and Dennis K. Berman

BODY:

Boston Scientific Corp., exploiting a monumental case of buyer's remorse by rival Johnson & Johnson, sealed a \$27 billion agreement to buy Guidant Corp. in an acquisition that creates a company set on dominating the field of cardiac devices.

The contest between Boston Scientific and J&J gave Wall Street something it hadn't seen in a while -- a large-scale bidding war that ended up putting an extra \$6 billion in Guidant investors' pockets.

The deal represents the biggest gamble in the history of Boston Scientific. The Natick, Mass., company has clawed its way into the big time in the health-care business with savvy acquisitions, hardball business tactics and a penchant for navigating threatening regulatory and legal shoals.

The combined company, with revenue of about \$9 billion, will have the No. 1 position in the U.S. in selling coronary stents, the tiny arterial implants that now dominate interventional cardiology. It also will have the No. 2 position in selling implantable defibrillators. These increasingly popular products rein in lethally fast heartbeats and have supplanted pacemakers as the main growth area in cardiac electrical therapy. Both products have rich profit margins and stand to benefit from an aging, overweight U.S. population.

Still, to finance the purchase, Boston Scientific will wind up with \$11 billion in debt, a burden that has already prompted rating agencies to put it on watch for a possible downgrade. It faces new competitors bringing stents to the market at a time when growth in the overall market has slowed.

Guidant, too, has been losing defibrillator share after recalls because of product malfunctions and ensuing federal investigations and patient lawsuits. Some analysts also see possible difficulties in gaining quick antitrust clearance for the deal.

Boston Scientific Faces Pivotal Test After Victory in Fight for Guidant

To help with antitrust clearance, Boston Scientific enlisted help from Abbott Laboratories, another big player in medical devices. Abbott will buy Guidant's stent business and other assets for \$4.1 billion, while Boston Scientific will retain shared rights to Guidant stent technology. Abbott will also purchase \$1 billion of Boston Scientific stock and lend Boston Scientific \$900 million.

Although confident that they can smoothly absorb Guidant and create a powerful health-care company, Boston Scientific executives have been so intensely focused on the bidding competition that celebrating a victorious outcome was nearly forgotten. As Chief Executive Officer James Tobin has put it in various conversations in the past several days, "We're kind of like the dog that caught the bus. Now what are we going to do with the bus?"

J&J sealed a deal to acquire Indianapolis-based Guidant last year. But it provided an opening for Boston Scientific to snatch away its prize when Guidant ran into its recall problems and J&J decided to trim its purchase price to \$63 a share from the previously agreed \$76. Boston Scientific intervened with its initial offer of \$72 a share on Dec. 5.

The bidding war culminated last week, when Guidant's board said Boston Scientific's \$80-a-share offer was preferable to a previous \$71-a-share offer from J&J. That gave J&J five days to sweeten its \$24 billion bid.

During those five days, tension mounted at Boston Scientific, where executives were forced into a waiting game to see what J&J would -- or would not -- do. Mr. Tobin would cut the tension by joking, "It's just a bunch of zeroes. You can't get tight just because it's billions."

They went to bed Tuesday night believing it was very possible that they were going to be aced out once again. No one slept much, especially Chairman Peter Nicholas, who had been traveling across multiple time zones during the bidding war and dealing with resultant jet lag.

Until Boston Scientific's last offer, they had been on the outside looking in, trying to decipher Guidant's true concerns. Each time Guidant chose a lower J&J bid over a higher Boston Scientific one, the Boston executives grew more frustrated as they sought to decipher "incomplete, cryptic information," as one Boston Scientific executive describes it. This was "a major frustration, and it raised the temperature in the room."

Even after Guidant last week declared Boston Scientific's \$27.2 billion offer "superior," J&J still had its five-day option. Rumors spread through the executive suites at both Boston Scientific and Guidant: First, that J&J wasn't coming back at all, then, that it was, but at \$76 a share, then \$78, then \$77.50, and finally, a whopping \$81 a share, with participation of a third party. According to this rumor, Medtronic Inc. would buy all or part of the Guidant stent business under a J&J deal. Medtronic officials say this didn't happen.

Boston Scientific executives had a meticulous response prepared for each eventuality. "What we weren't prepared for was silence," says one executive on the Boston Scientific side. Boston Scientific executives thought they would hear Tuesday afternoon at 4 p.m., then at 5. Then they were sure they would get definitive documents to sign at 12:02 a.m. yesterday. That didn't happen, and they feared the worst.

At 6:27 a.m. yesterday, an email arrived from Boston Scientific's lawyers, Shearman & Sterling. Boston Scientific had won.

In 4 p.m. New York Stock Exchange composite trading yesterday, Guidant shares fell \$1.59, or 2.1%, to \$75.19. Boston Scientific shares were down 46 cents, or 1.9%, at \$23.54. J&J shares were down 86 cents, or 1.5%, at \$58.50.

Boston Scientific was formed in 1979 by John Abele, an inventor who believed in the promise of less-invasive surgery, and Mr. Nicholas, a former Eli Lilly & Co. executive. The purpose of the start-up: buying Medi-Tech Inc., Mr. Abele's employer.

The two scraped together \$300,000 and persuaded some Boston bankers to lend them \$500,000 more to purchase

Boston Scientific Faces Pivotal Test After Victory in Fight for Guidant

Medi-Tech, a maker of catheters, cell-sampling tools and depilatories. In the early days, Boston Scientific grew by using its expertise in catheters to make the tools "larger or shorter, fatter or smaller," depending on how they were to be used, says venture capitalist Thomas Brooks, who joined the company in 1986 when it was still privately held and had fewer than 100 employees.

With a fresh infusion of cash from its 1992 initial public offering, Boston Scientific went on an acquisition binge. The most important purchase was SciMed Life Systems Inc., a successful manufacturer of angioplasty balloons and catheters. Boston Scientific bought it in 1995 for about \$850 million in stock.

While that figure pales next to the \$27 billion price Boston Scientific will pay for Guidant, the two transactions share one crucial similarity: their ability to catapult Boston Scientific into the top tier of a chosen market. SciMed instantly turned Boston Scientific into one of the leading manufacturers of angioplasty balloons and other products in interventional cardiology. As the likely No. 1 in the market for cardiac devices, Boston Scientific will go head-to-head with current market leader Medtronic.

Driven by Mr. Nicholas, Boston Scientific has bought more than 25 companies in the past 10 years, growing to about 16,000 employees and annual revenue of more than \$6 billion. With Guidant, it will acquire 12,000 employees and about \$3.6 billion in annual revenue.

The bid for Guidant is being bankrolled, in essence, by Boston Scientific's success in coronary stents. In 2004, Boston Scientific orchestrated one of the most successful product launches in the history of the medical-device industry when it got Food and Drug Administration approval for its Taxus Express drug-coated stent. The drug coating reduces the chance that a buildup of cells around the stent -- called "restenosis" -- will relog the artery. At the time, J&J was the only company with a drug-coated stent in the U.S.

Boston Scientific made a bold prediction: Taxus would garner 70% of the market in 70 days.

It did better than that, snatching away the lead from J&J and attaining 70% market share within 17 days, according to a company spokesperson. The company posted a 62% revenue increase for 2004, despite a recall of about 99,000 Taxus stents that summer due to malfunctions that caused several injuries and deaths.

The company saw its prospects sour in 2005 as U.S. market share for the stent started to erode -- down to about 54% now -- amid safety concerns about Taxus and a resurgence in popularity for J&J's Cypher. Since their peak in 2004, shares of Boston Scientific are down more than 40%.

Boston Scientific officials believe that Guidant, while damaged by the recall, pending litigation and lost share, will rebound within perhaps a year. The \$10 billion business of making defibrillators is growing at a rate of 20% a year. In addition, Guidant's program to produce a stent coated with a drug called everolimus is considered a potentially important one. Guidant's stent is considered easily maneuverable by cardiologists who use it.

Guidant will expose its acquirer to risks of unknown dimension stemming from the company's defibrillator recalls and alleged hiding of problems. Guidant faces a federal investigation by the U.S. Attorney's office in Minneapolis, among other pressures.

Boston Scientific itself fell under a lengthy Justice Department criminal investigation for allegedly shipping stents it knew to be defective. The matter ended last summer in a civil complaint and settlement reached with the U.S. Attorney in Boston. Despite testing that revealed failures at "unacceptably high rates," management at the company decided to continue shipping the stents, the complaint said. In the settlement, Boston Scientific paid \$74 million and made no admission of guilt.

Boston Scientific will confront a few hurdles as it subsumes Guidant's products and operations. Among the issues: The deal will give Boston Scientific two drug-coated stents -- its own, which uses the drug paclitaxel, and the

Boston Scientific Faces Pivotal Test After Victory in Fight for Guidant

forthcoming everolimus stent.

Some analysts worry that Boston Scientific's proposed arrangement with Abbott Laboratories may not be enough to ward off antitrust concerns. In that case, Boston Scientific may have to distance itself further from the Guidant stent technology, perhaps by selling it entirely.

Complete divestment of Guidant's drug-coated stent technology is "an extremely low likelihood," says Paul Donovan, a spokesman for Boston Scientific. He adds that the company expects the FTC to clear the deal by March 31, with the technology-sharing arrangement.

Another potential wrinkle arises in the intellectual-property rights surrounding stents -- an area that's been the subject of extensive litigation in the industry. Citigroup analyst Matthew Dodds says J&J holds patents on methods of using "limus"-type drugs on stents -- including the everolimus on Guidant's stent, as well as a drug on an Abbott stent.

Now that J&J has lost the battle for Guidant, it isn't likely to license the technology to either Guidant or Abbott, and that could slow down the deal, Mr. Dodds says. "If these patents block a limus, you don't really have" a drug-coated stent program, he says. That would leave only J&J, Boston Scientific and, to a lesser extent, Medtronic, as potential players in the market, a situation that could trouble antitrust reviewers. Mr. Dodds predicts that J&J is "going to make this a big issue with the FTC. . . . They are not incentivized to let them close the deal quickly."

But Boston Scientific's Mr. Donovan says: "We do not consider this to be an issue"

Charles Forelle contributed to this article.

Online Today: WSJ.com subscribers can track Guidant's share price, and see how the company stacks up against Boston Scientific, at WSJ.com/OnlineToday.

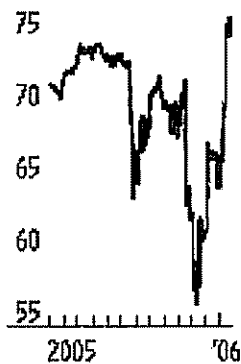
Boston Scientific Faces Pivotal Test After Victory in Fight for Guidant

Page 5

Vital Signs

Guidant's stock price:

\$80



Source: WSI Market
Data Group

NOTES:

PUBLISHER: Dow Jones & Company, Inc.

LOAD-DATE: January 26, 2006

Exhibit R

PATENT

DOCKET NO.: CRDS-0005(JJI-51-CON2)

Application No.: 10/951,385



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Carol Wright, et al.

Confirmation No.: 7537

Application No.: 10/951,385

Group Art Unit: 3731

Filing Date: September 28, 2004

Examiner:

For: Local Delivery of Rapamycin for Treatment of Proliferative Sequelae
Associated with PTCA Procedures, Including Delivery Using a Modified Stent

08/09/2006 HDESTAL 00000002 10951385

01 FC:1464

130.00 OP

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT
(37 CFR § 1.102 and MPEP § 708.02)

Applicant hereby petitions to make this application special because of actual infringement.

1. Accompanying material

Accompanying this petition is:

- a. A Declaration by Attorney in Support of Petition to Make Special Because of Actual Infringement; and
- b. Supplemental Information Disclosure Statement.

2. Fee (37 CFR § 1.17(i))

The fee required is to be paid by:

☒ A check in the amount of \$130.00 is attached.

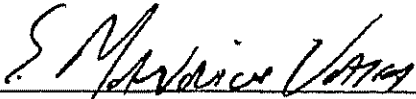
DOCKET NO.: CRDS-0005(JJI-51-CON2)

PATENT

Application No.: 10/951,385

- ☐ Please charge Deposit Account No. 23-3050 in the amount of \$130.00. This sheet is attached in duplicate.
- ☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

Date: August 7, 2006


S. Maurice Valla
Registration No. 43,966

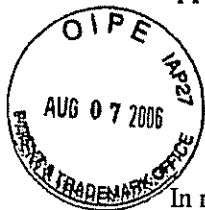
Woodcock Washburn LLP
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DOCKET NO.: CRDS-0005(JJI-51-CON2)

PATENT

Application No.: 10/951,385



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Carol Wright, et al.

Confirmation No.: 7537

Application No.: 10/951,385

Group Art Unit: 3731

Filing Date: September 28, 2004

Examiner: Not yet assigned

For: **Local Delivery of Rapamycin for Treatment of Proliferative Sequelae
Associated with PTCA Procedures, Including Delivery Using a Modified Stent**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

**DECLARATION BY ATTORNEY IN SUPPORT OF PETITION TO MAKE
SPECIAL BECAUSE OF ACTUAL INFRINGEMENT (MPEP § 708.02)**

I, S. Maurice Valla, Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia PA, 19103, Registration No. 43,966, Telephone No. 215-564-3100, am the attorney of record for Applicants and make the following declarations.

1. The instant application is directed to drug-eluting stents. Claims 64 to 140 are presently pending. Claims 64 and 103 are the only independent claims. Claim 103 is directed to a device comprising a metallic stent, a biocompatible polymeric carrier and a drug. The drug is rapamycin or a macrocyclic lactone analog thereof and is present in an amount effective to inhibit neointimal proliferation. Claim 130, which depends from claim 103, specifies that the drug is a macrocyclic lactone analog of rapamycin.

ABT 008006

DOCKET NO.: CRDS-0005(JJI-51-CON2)
Application No.: 10/951,385

PATENT

2. Attached as exhibits hereto are press releases issued by Guidant Corporation ("Guidant") describing its activities relating to drug eluting stents. In a release dated January 30, 2006 (Exhibit 1), Guidant announced that it has received Conformité Européene (CE) Mark Approval for its XIENCE™ V Everolimus Eluting Coronary Stent System. In the same press release, Guidant states that it "is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE™ V beginning in the second quarter of 2006."

3. In a release dated October 19, 2005 (Exhibit 2), Guidant announced that inspection of its manufacturing facilities in Temecula, California had been successfully concluded as part of its submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. Guidant reported that its European Notified Body found no nonconformities and would recommend certification for Guidant's manufacturing facility for XIENCE™ V.

4. Since Guidant's approved manufacturing facility for XIENCE™ V is in Temecula, California, I conclude that the "ramping up manufacturing and building inventory to . . . support the European launch of XIENCE™ V" to which Guidant's January 30, 2006, release refers is being performed in the United States. Thus, on the basis of these public statements by Guidant, I conclude that Guidant is "making" XIENCE™ V and building inventory in the United States to support launch of the product in Europe.

5. Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

6. I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases, with the claims of the instant application. In my opinion, the XIENCE™ V

DOCKET NO.: CRDS-0005(JJI-51-CON2)
Application No.: 10/951,385

PATENT

product is unquestionably within the scope of at least claims 103 and 130 on file in this application.

7. In a release dated September 21, 2005 (Exhibit 5), Guidant states that XIENCE™ V is being utilized in SPIRIT II and SPIRIT III clinical trials to evaluate the safety and efficacy of the product for the treatment of coronary artery disease. XIENCE™ V is described as “an everolimus eluting coronary stent system utilizing Guidant’s cobalt chromium MULTI-LINK VISION® Coronary Stent System platform.” In an earlier release, dated April 5, 2004 (Exhibit 6), Guidant stated that it “holds a worldwide exclusive license . . . to use everolimus, a novel proliferation-signal inhibitor with potent anti-proliferative and immunosuppressant properties, in drug eluting stents.” The April 5, 2004, release also states that “Guidant has both durable and bioabsorbable polymer drug carriers in development” and that “[t]he company’s clinical trials utilizing durable polymer technology are identified by the SPIRIT designation in the study name.” In the same press release, the MULTI-LINK VISION® Coronary Stent System is referred to as a “market-leading metallic stent.” On the basis of these statements made by Guidant, I conclude that the XIENCE™ V product comprises a metallic stent coated with everolimus and a durable polymer carrier.

8. Everolimus is a macrocyclic lactone analog of rapamycin, bearing a stable 2-hydroxyethyl chain substitution at position 40 on the rapamycin structure (Exhibits 7, 8). In a press release dated March 15, 2006 (Exhibit 9), Guidant stated “everolimus has been shown to reduce tissue proliferation in the coronary vessels following stent implantation.” Similarly, in a release dated November 15, 2005 (Exhibit 10), Guidant stated that “[t]he one year data from SPIRIT FIRST continued to demonstrate a preservation of the treatment effect of the XIENCE V Everolimus Eluting Coronary Stent System, with a highly statistically significant reduction of cell proliferation compared to the uncoated control.” On the basis of the known structure of everolimus and Guidant’s statements, I conclude that the XIENCE™ V product contains a macrocyclic lactone analog of rapamycin in an amount effective to inhibit neointimal proliferation.

DOCKET NO.: CRDS-0005(JJI-51-CON2)
Application No.: 10/951,385

PATENT

9. It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of at least claims 103 and 130 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.


10. I have a knowledge of the pertinent prior art by virtue of the prosecution histories of the parents of the instant application and other patents owned by the assignee of the instant application. All such material art is provided to the Examiner as

- ☒ having been filed
- ☒ being filed

in a respective Information Disclosure Statement.

10. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: August 7, 2006


S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

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Exhibit S

DOCKET NO.: CRDS-0066
Application No.: Not yet assigned

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Carol Wright, et al.

Confirmation No.: **Not yet assigned**

Application No.: **Not yet assigned**

Group Art Unit: **Not yet assigned**

Filing Date: **August 24, 2006**

Examiner: **Not yet assigned**

For: **Local Delivery of Rapamycin for Treatment of Proliferative Sequelae
Associated with PTCA Procedures, Including Delivery Using a Modified Stent**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT
(37 CFR § 1.102 and MPEP § 708.02)

Applicant hereby petitions to make this application special because of actual infringement.

1. Accompanying material

Accompanying this petition is:

A Declaration by Attorney in Support of Petition to Make Special Because of Actual Infringement, with Exhibits 1-9.

2. Fee (37 CFR § 1.17(i))

The fee required is to be paid by:

DOCKET NO.: CRDS-0066

PATENT

Application No.: Not yet assigned

- ☐ A check in the amount of \$130.00 is attached.
- ☒ Please charge Deposit Account No. 23-3050 in the amount of \$130.00.
- ☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

DATE: August 24, 2006

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
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DOCKET NO.: CRDS-0066
Application No.: Not yet assigned

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Carol Wright, et al.

Confirmation No.:

Application No.: not yet assigned

Group Art Unit:

Filing Date: August 15, 2006

Examiner: Not yet assigned

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Associated with PTCA Procedures, Including Delivery Using a Modified Stent**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

**DECLARATION BY ATTORNEY IN SUPPORT OF PETITION TO MAKE SPECIAL
BECAUSE OF ACTUAL INFRINGEMENT (MPEP § 708.02)**

I, S. Maurice Valla, Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia PA, 19103, Registration No. 43,966, Telephone No. 215-564-3100, am the attorney of record for Applicants and make the following declarations.

1. The instant application is directed to drug-eluting stents. Claims 1 to 5 are presently pending. Claim 1, the only independent claim, is directed to a metallic stent having a coating applied thereto. The coating comprises a mixture of a polymeric carrier and a therapeutic agent that is rapamycin or a macrocyclic lactone analog thereof and is present in an amount effective to inhibit neointimal proliferation. The device provides a controlled release of the therapeutic agent

DOCKET NO.: CRDS-0066**PATENT****Application No.:** Not yet assigned

over a period of several weeks. Claim 2 recites that the therapeutic agent is a macrocyclic lactone analog of rapamycin, claim 3 recites that the polymeric carrier comprises a fluorinated polymer, and claim 4 recites a polymeric carrier that further comprises an acrylate-based polymer or copolymer. Claim 5 is directed to a method for inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty that comprises implanting a metallic stent according to any one of claims 1 to 4 in the lumen of said coronary artery.

2. Attached as exhibits hereto are several press releases issued by Guidant Corporation ("Guidant") describing its activities relating to drug eluting stents. In a release dated January 30, 2006 (Exhibit 1), Guidant announced that it has received Conformité Européene (CE) Mark Approval for its XIENCE™ V Everolimus Eluting Coronary Stent System. In the same press release, Guidant states that it "is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE™ V beginning in the second quarter of 2006."

3. In a release dated October 19, 2005 (Exhibit 2), Guidant announced that inspection of its manufacturing facilities in Temecula, California had been successfully concluded as part of its submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. Guidant reported that its European Notified Body found no nonconformities and would recommend certification for Guidant's manufacturing facility for XIENCE™ V.

4. Since Guidant's approved manufacturing facility for XIENCE™ V is in Temecula, California, I conclude that the "ramping up manufacturing and building inventory to . . . support the European launch of XIENCE™ V" to which Guidant's January 30, 2006, release refers is being performed in the United States. Thus, on the basis of these public statements by Guidant, I

DOCKET NO.: CRDS-0066

PATENT

Application No.: Not yet assigned

conclude that Guidant is "making" XIENCE™ V and building inventory in the United States to support launch of the product in Europe.

5. Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

6. I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of claims 1 to 5 on file in this application.

7. Abbott's Fact Sheet attached hereto as Exhibit 4 further states that the XIENCE™ V product elutes everolimus from a MULTI-LINK VISION metallic stent. Everolimus is a macrocyclic lactone analog of rapamycin, bearing a stable 2-hydroxyethyl chain substitution at position 40 on the rapamycin structure (Exhibits 5, 6). In a press release dated March 15, 2006 (Exhibit 7), Guidant stated "everolimus has been shown to reduce tissue proliferation in the coronary vessels following stent implantation." Similarly, in a release dated November 15, 2005 (Exhibit 8), Guidant stated that "[t]he one year data from SPIRIT FIRST continued to demonstrate a preservation of the treatment effect of the XIENCE V Everolimus Eluting Coronary Stent System, with a highly statistically significant reduction of cell proliferation compared to the uncoated control." On the basis of the known structure of everolimus and Guidant's statements, I conclude that the XIENCE™ V product comprises a metallic stent and a macrocyclic lactone analog of rapamycin in an amount effective to inhibit neointimal proliferation.

DOCKET NO.: CRDS-0066
Application No.: Not yet assigned

PATENT

8. An article published in EuroIntervention in 2005 (Exhibit 9) confirms the XIENCE™ V product comprises a stent bearing a coating that comprises a nonerodible (*i.e.*, nonabsorbable) polymer blended with everolimus (page 59, col. 2). The coating is said to include a blend of acrylic and fluoro polymers, and the article further states that the stent is designed to release approximately 70% of the drug within 30 days after implantation (*Id.*). On the basis of this information, I conclude that the XIENCE™ V product comprises a nonerodible polymeric coating comprising a fluropolymer and an acrylate-based polymer affixed to a metallic stent, and a macrocyclic triene analog of rapamycin incorporated into the coating. I further concluded that the XIENCE™ V product provides a controlled release of the therapeutic agent over a period of several weeks, as recited in claims 1 to 4.

9. The EuroIntervention article cited above (Exhibit 9) further confirms that the XIENCE™ V product is intended for use in a method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty (*see Id.*), as recited in claim 5 of the instant application.

10. It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of claims 1 to 5 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

11. I have a knowledge of the pertinent prior art by virtue of the prosecution histories of the parents of the instant application and other patents owned by the assignee of the instant application. All such material art is provided to the Examiner as

- ☐ having been filed
- ☒ being filed

in a respective Information Disclosure Statement.

DOCKET NO.: CRDS-0066

PATENT

Application No.: Not yet assigned

12. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATE: August 24, 2006

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

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Exhibit T

DOCKET NO.: CRDS-0067
Application No.: Not yet assigned

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Carol Wright, et al.

Confirmation No.: Not yet assigned

Application No.: Not yet assigned

Group Art Unit: Not yet assigned

Filing Date: August 24, 2006

Examiner: Not yet assigned

For: **Local Delivery of Rapamycin for Treatment of Proliferative Sequelae
Associated with PTCA Procedures, Including Delivery Using a Modified Stent**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT
(37 CFR § 1.102 and MPEP § 708.02)

Applicant hereby petitions to make this application special because of actual infringement.

1. Accompanying material

Accompanying this petition is:

- a. A Declaration by Attorney in Support of Petition to Make Special Because of Actual Infringement with Exhibits 1-9.

2. Fee (37 CFR § 1.17(i))

DOCKET NO.: CRDS-0067

PATENT

Application No.: Not yet assigned

The fee required is to be paid by:

- ☐ A check in the amount of \$130.00 is attached.
- ☒ Please charge Deposit Account No. 23-3050 in the amount of \$130.00.
- ☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

DATE: August 24, 2006

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

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One Liberty Place - 46th Floor
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DOCKET NO.: CRDS-0067
Application No.: Not yet assigned

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Carol Wright, et al.	Confirmation No.:
Application No.: not yet assigned	Group Art Unit:
Filing Date: August 15, 2006	Examiner: Not yet assigned
For: Local Delivery of Rapamycin for Treatment of Proliferative Sequelae Associated with PTCA Procedures, Including Delivery Using a Modified Stent	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

**DECLARATION BY ATTORNEY IN SUPPORT OF PETITION TO MAKE SPECIAL
BECAUSE OF ACTUAL INFRINGEMENT (MPEP § 708.02)**

I, S. Maurice Valla, Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia PA, 19103, Registration No. 43,966, Telephone No. 215-564-3100, am the attorney of record for Applicants and make the following declarations.

1. The instant application is directed to drug-eluting stents. Claims 1 to 5 are presently pending. Claim 1, the only independent claim, is directed to device comprising a metallic stent having a nonabsorbable polymeric carrier, and a therapeutic agent. The polymeric carrier comprises an acrylate-based polymer or copolymer, a fluorinated polymer, or a mixture thereof. The therapeutic agent is rapamycin or a macrocyclic lactone analog thereof and is present in an

DOCKET NO.: CRDS-0067**PATENT****Application No.:** Not yet assigned

amount effective to inhibit neointimal proliferation. Claim 2 recites that the therapeutic agent is a macrocyclic lactone analog of rapamycin, and claims 3 and 4 recite that the device provides a controlled release of the therapeutic agent over a period of several weeks. Claim 5 is directed to a method for inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty that comprises implanting a device according to any one of claims 1 to 4 in the lumen of said coronary artery.

2. Attached as exhibits hereto are several press releases issued by Guidant Corporation ("Guidant") describing its activities relating to drug eluting stents. In a release dated January 30, 2006 (Exhibit 1), Guidant announced that it has received Conformité Européene (CE) Mark Approval for its XIENCE™ V Everolimus Eluting Coronary Stent System. In the same press release, Guidant states that it "is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE™ V beginning in the second quarter of 2006."

3. In a release dated October 19, 2005 (Exhibit 2), Guidant announced that inspection of its manufacturing facilities in Temecula, California had been successfully concluded as part of its submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. Guidant reported that its European Notified Body found no nonconformities and would recommend certification for Guidant's manufacturing facility for XIENCE™ V.

4. Since Guidant's approved manufacturing facility for XIENCE™ V is in Temecula, California, I conclude that the "ramping up manufacturing and building inventory to . . . support the European launch of XIENCE™ V" to which Guidant's January 30, 2006, release refers is being performed in the United States. Thus, on the basis of these public statements by Guidant, I

DOCKET NO.: CRDS-0067

PATENT

Application No.: Not yet assigned

conclude that Guidant is "making" XIENCE™ V and building inventory in the United States to support launch of the product in Europe.

5. Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

6. I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of claims 1 to 5 on file in this application.

7. Abbott's Fact Sheet attached hereto as Exhibit 4 further states that the XIENCE™ V product elutes everolimus from a MULTI-LINK VISION metallic stent. Everolimus is a macrocyclic lactone analog of rapamycin, bearing a stable 2-hydroxyethyl chain substitution at position 40 on the rapamycin structure (Exhibits 5, 6). In a press release dated March 15, 2006 (Exhibit 7), Guidant stated "everolimus has been shown to reduce tissue proliferation in the coronary vessels following stent implantation." Similarly, in a release dated November 15, 2005 (Exhibit 8), Guidant stated that "[t]he one year data from SPIRIT FIRST continued to demonstrate a preservation of the treatment effect of the XIENCE V Everolimus Eluting Coronary Stent System, with a highly statistically significant reduction of cell proliferation compared to the uncoated control." On the basis of the known structure of everolimus and Guidant's statements, I conclude that the XIENCE™ V product is a device that comprises a metallic stent and a macrocyclic lactone analog of rapamycin in an amount effective to inhibit neointimal proliferation.

DOCKET NO.: CRDS-0067

PATENT

Application No.: Not yet assigned

8. An article published in EuroIntervention in 2005 (Exhibit 9) confirms the XIENCE™ V product comprises a nonerodible (*i.e.*, nonabsorbable) polymeric carrier that includes a blend of acrylic and fluoro polymers (*Id.*). The article further states that the stent is designed to release approximately 70% of the drug within 30 days after implantation. On the basis of this information, I conclude that the XIENCE™ V product comprises a nonerodible polymeric carrier comprising both a fluropolymer and an acrylate-based polymer, and that it provides a controlled release of the therapeutic agent over a period of several weeks, as recited in claims 1 to 4 of the instant application.

9. The EuroIntervention article cited above (Exhibit 9) further confirms that the XIENCE™ V product is intended for use in a method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty (*see Id.*), as recited in claim 5 of the instant application.

10. It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of claims 1 to 5 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

11. I have a knowledge of the pertinent prior art by virtue of the prosecution histories of the parents of the instant application and other patents owned by the assignee of the instant application. All such material art is provided to the Examiner as

☐ having been filed

☒ being filed

in a respective Information Disclosure Statement.

DOCKET NO.: CRDS-0067
Application No.: Not yet assigned

PATENT

12. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATE: August 24, 2006

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
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Exhibit U

DOCKET NO.: CRDS-0062 (CRD0931CIP)
Application No.: 10/829,074

PATENT



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Robert Falotico, et al.

Confirmation No.: 5950

Application No.: 10/829,074

Group Art Unit: 3743

Filing Date: April 21, 2004

Examiner: Not yet assigned

For: **Drug/Drug Delivery Systems for the Prevention and Treatment of Vascular Disease**

08/09/2006 HDESTA1 00000001 10829074

04 FC:1464

130.00 DP

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT
(37 CFR § 1.102 and MPEP § 708.02)

Applicant hereby petitions to make this application special because of actual infringement.

1. Accompanying material

Accompanying this petition is:

- a. A Declaration by Attorney in Support of Petition to Make Special Because of Actual Infringement; and
- b. Supplemental Information Disclosure Statement.

2. Fee (37 CFR § 1.17(i))

The fee required is to be paid by:

- ☒ A check in the amount of \$130.00 is attached.

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ABT 006995

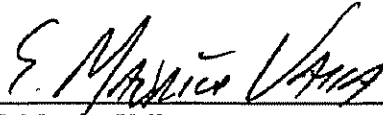
Abbott Laboratories and Advanced Cardiovascular Systems, Inc. v Johnson and Johnson, Inc. and Cordis Corporation DEDC C.A. No. 06-613-SLR.

DOCKET NO.: CRDS-0062 (CRD0931CIP)
Application No.: 10/829,074

PATENT

- ☐ Please charge Deposit Account No. 23-3050 in the amount of \$130.00. This sheet is attached in duplicate.
- ☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

Date: August 7, 2006


S. Maurice Valla
Registration No. 43,966

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DOCKET NO.: CRDS-0062 (CRD0931CIP)
Application No.: 10/829,074

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Robert Falotico, et al.

Confirmation No.: 5950

Application No.: 10/829,074

Group Art Unit: 3743

Filing Date: April 21, 2004

Examiner: Not yet assigned

For: **Drug/Drug Delivery Systems for the Prevention and Treatment of Vascular Disease**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

**DECLARATION BY ATTORNEY IN SUPPORT OF PETITION TO MAKE
SPECIAL BECAUSE OF ACTUAL INFRINGEMENT (MPEP § 708.02)**

I, S. Maurice Valla, Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia PA, 19103, Registration No. 43,966, Telephone No. 215-564-3100, am the attorney of record for Applicants and make the following declarations.

1. Claims 15 to 30 are presently pending. Each of the claims is directed to devices comprising an intraluminal stent, a nonerodible polymeric coating affixed to the stent, and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the coating; the devices provide an in-stent late loss in diameter at 12 months following implantation in a human of less than about 0.5 mm, as measured by quantitative coronary angiography. Claim 16 specifies an in-stent late loss in diameter of less than about 0.3 mm, and claims 17 and 18 specify that the stent provides an in-stent diameter stenosis at 12 months following implantation in a human of less than about 22% or 15%, respectively, as

DOCKET NO.: CRDS-0062 (CRD0931CIP)
Application No.: 10/829,074

PATENT

measured by quantitative coronary angiography. Claims 19 to 22 are similar to claims 15 to 18, but specify mean in-stent late loss and in-stent diameter stenosis values for in a human population. Claims 23 to 30 are directed to methods of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty, comprising implanting in the lumen of said coronary artery a drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating. These methods provide in-stent late loss and/or in-stent diameter stenosis values as recited in claims 15 to 22.

2. Attached as exhibits hereto are press releases issued by Guidant Corporation ("Guidant") describing certain of its activities relating to drug eluting stents. In a release dated January 30, 2006 (Exhibit 1), Guidant announced that it has received Conformité Européene (CE) Mark Approval for its XIENCE™ V Everolimus Eluting Coronary Stent System. In the same press release, Guidant states that it "is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE™ V beginning in the second quarter of 2006."

3. In a release dated October 19, 2005 (Exhibit 2), Guidant announced that inspection of its manufacturing facilities in Temecula, California had been successfully concluded as part of its submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. Guidant reported that its European Notified Body found no nonconformities and would recommend certification for Guidant's manufacturing facility for XIENCE™ V.

4. Since Guidant's approved manufacturing facility for XIENCE™ V is in Temecula, California, I conclude that the "ramping up manufacturing and building inventory to . . . support the European launch of XIENCE™ V" to which Guidant's January 30, 2006, release refers is being performed in the United States. Thus, on the basis of these public statements by Guidant, I conclude that Guidant is "making" XIENCE™ V and building inventory in the United States to support launch of the product in Europe.

DOCKET NO.: CRDS-0062 (CRD0931CIP)
Application No.: 10/829,074

PATENT

5. Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

6. I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases and other publicly available documents, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of claims 15 to 30 on file in this application.

7. Everolimus is a macrocyclic triene analog of rapamycin, bearing a stable 2-hydroxyethyl chain substitution at position 40 on the rapamycin structure (Exhibits 5,6). An article published in EuroIntervention in 2005 (Exhibit 7) confirms that everolimus binds with FKBP12 (*see* page 59, col. 1), and that XIENCE™ V product comprises a stent bearing a coating that comprises a nonerodible polymer blended with everolimus (*see* page 59, col. 2). On the basis of this information, I conclude that the XIENCE™ V product comprises an intraluminal stent, a nonerodible polymeric coating affixed to the stent, and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the coating, as recited in claims 15 to 30 on file in this application.

8. Another article published in EuroIntervention in 2005 (Exhibit 8) reports on one-year results from Guidant's SPIRIT FIRST clinical trial, in which intravascular ultrasound and quantitative angiographic analyses were performed one year following intraluminal implantation of XIENCE™ V stents in the coronary arteries of human patients. The article reports that mean in-stent late loss and diameter stenosis values were 0.24mm and 18%, respectively (*see* abstract), which is within the limits recited in claims 15 to 30 on file in this application.

9. It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of claims 15 to 30 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

DOCKET NO.: CRDS-0062 (CRD0931CIP)
Application No.: 10/829,074

PATENT


10. I have a knowledge of the pertinent prior art by virtue of the prosecution histories of the parents of the instant application and other patents owned by the assignee of the instant application. All such material art is provided to the Examiner as

- ☒ having been filed
- ☒ being filed

in a respective Information Disclosure Statement.

11. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: August 7, 2006



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f

Exhibit V

DOCKET NO.: CRDS-0064 (CRD0932CIP)
Application No.: 10/852,517

PATENT



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Robert Falotico, et al.

Confirmation No.: 4554

Application No.: 10/852,517

Group Art Unit: 3743

Filing Date: May 24, 2004

Examiner: Not yet assigned

For: ANTIPROLIFERATIVE DRUG AND DELIVERY DEVICE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT
(37 CFR § 1.102 and MPEP § 708.02)

Applicant hereby petitions to make this application special because of actual infringement.

1. Accompanying material

Accompanying this petition is:

- a. A Declaration by Attorney in Support of Petition to Make Special Because of Actual Infringement; and
- b. Supplemental Information Disclosure Statement.

2. Fee (37 CFR § 1.17(i))

The fee required is to be paid by:

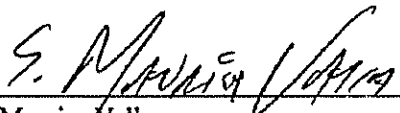
- ☒ A check in the amount of \$130.00 is attached.

DOCKET NO.: CRDS-0064 (CRD0932CIP)
Application No.: 10/852,517

PATENT

- ☐ Please charge Deposit Account No. 23-3050 in the amount of \$130.00. This sheet is attached in duplicate.
- ☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

Date: August 7, 2006


S. Maurice Valla
Registration No. 43,966

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DOCKET NO.: CRDS-0064 (CRD0932CIP)

PATENT

Application No.: 10/852,517



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Robert Falotico, et al.

Confirmation No.: 4554

Application No.: 10/853,517

Group Art Unit: 3743

Filing Date: May 24, 2004

Examiner: Not yet assigned

For: ANTIPROLIFERATIVE DRUG AND DELIVERY DEVICE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION BY ATTORNEY IN SUPPORT OF PETITION TO MAKE
SPECIAL BECAUSE OF ACTUAL INFRINGEMENT (MPEP § 708.02)

I, S. Maurice Valla, Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia PA, 19103, Registration No. 43,966, Telephone No. 215-564-3100, am the attorney of record for Applicants and make the following declarations.

1. Claims 5 to 9 are presently pending. These claims are directed to drug delivery devices and methods of using same. The devices comprise: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and a therapeutic dosage of a macrocyclic triene analog of rapamycin that binds FKBP12 and is incorporated into the polymeric coating; a portion of the therapeutic dosage is released during a period of about two weeks to about six weeks following intraluminal implantation. Claim 8 is directed to methods of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting the claimed drug delivery device in the lumen of said coronary artery. Claim 9, which depends from

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ABT 007343

DOCKET NO.: CRDS-0064 (CRD0932CIP)
Application No.: 10/852,517

PATENT

claim 8, is directed to methods of this type that provide a reduction in in-stent neointimal hyperplasia that is present for at least one year following intraluminal implantation of the device.

2. Attached as exhibits hereto are press releases issued by Guidant Corporation ("Guidant") describing certain of its activities relating to drug eluting stents. In a release dated January 30, 2006 (Exhibit 1), Guidant announced that it received Conformité Européene (CE) Mark Approval for its XIENCE™ V Everolimus Eluting Coronary Stent System. In the same press release, Guidant states that it "is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE™ V beginning in the second quarter of 2006" (*Id.*).

3. In a release dated October 19, 2005 (Exhibit 2), Guidant announced that inspection of its manufacturing facilities in Temecula, California had been successfully concluded as part of its submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. Guidant reported that its European Notified Body found no nonconformities and would recommend certification for Guidant's manufacturing facility for XIENCE™ V (*Id.*).

4. Because Guidant announced that its approved manufacturing facility for the XIENCE™ V product is in Temecula, California, I conclude that the "ramping up manufacturing and building inventory to . . . support the European launch of XIENCE™ V" to which Guidant's January 30, 2006, release refers is being performed in the United States. Thus, on the basis of these public statements by Guidant, I conclude that Guidant is "making" the XIENCE™ V product and building inventory in the United States to support launch of the product in Europe.

5. Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch the XIENCE™ V product in Europe in the third quarter of 2006 (Exhibit 4).

6. I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases and other publicly available documents, with the claims of the instant

DOCKET NO.: CRDS-0064 (CRD0932CIP)
Application No.: 10/852,517

PATENT

application. In my opinion, the XIENCE™ V product is unquestionably within the scope of claims 4, 7 and 8 on file in this application.

7. Everolimus is a macrocyclic triene analog of rapamycin, bearing a stable 2-hydroxyethyl chain substitution at position 40 on the rapamycin structure (Exhibits 5, 6). An article published in EuroIntervention in 2005 (Exhibit 7) confirms that everolimus binds with FKBP12 (page 59, col. 1), and that the XIENCE™ V product comprises a stent bearing a coating that comprises a nonerodible polymer blended with everolimus (page 59, col. 2). The article further states that the stent is designed to release approximately 70% of the drug within 30 days after implantation (*Id.*). On the basis of this information, I conclude that the XIENCE™ V product comprises an intraluminal stent, a nonerodible polymeric coating affixed to the stent, and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the coating, and releases a portion of the drug during a period of about two weeks to about six weeks, as recited claims on file in this patent application.

8. Another EuroIntervention article (Exhibit 8) reports on one-year results from Guidant's SPIRIT FIRST clinical trial, in which intravascular ultrasound and quantitative angiographic analyses were performed one year following intraluminal implantation of XIENCE™ V stents in the coronary arteries of human patients. The article reports that the stents provide reductions in in-stent late loss and diameter stenosis, two frequently cited indicators of neointimal hyperplasia, that is present at one year following implantation (*see* abstract), as recited in claim 8 of this patent application.

9. It is therefore my opinion that the product Guidant in the United States to support the European launch is unquestionably within the scope of at least claims 5, 8 and 9 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

10. I have a knowledge of the pertinent prior art by virtue of the prosecution histories of the parents of the instant application and other patents owned by the assignee of the instant application. All such material art is provided to the Examiner as

- ☒ having been filed
- ☒ being filed


DOCKET NO.: CRDS-0064 (CRD0932CIP)
Application No.: 10/852,517

PATENT

in a respective Information Disclosure Statement.

11. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: August 7, 2006


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Registration No. 43,966

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Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

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Exhibit W

DOCKET NO.: CRDS-0068
Application No.: Not yet assigned

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Confirmation No.:
Robert Falotico, et al.	Not yet assigned
Application No.:	Group Art Unit:
Not yet assigned	Not yet assigned
Filing Date: August 24, 2006	Examiner: Not yet assigned
For: Drug/Drug Delivery Systems for the Prevention and Treatment of Vascular Disease	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO MAKE SPECIAL BECAUSE OF ACTUAL INFRINGEMENT
(37 CFR § 1.102 and MPEP § 708.02)

Applicant hereby petitions to make this application special because of actual infringement.

1. Accompanying material

Accompanying this petition is:

- a. A Declaration by Attorney in Support of Petition to Make Special Because of Actual Infringement with Exhibits 1-8.

2. Fee (37 CFR § 1.17(i))

The fee required is to be paid by:

- ☐ A check in the amount of \$130.00 is attached.

DOCKET NO.: CRDS-0068

PATENT

Application No.: Not yet assigned

- ☒ Please charge Deposit Account No. 23-3050 in the amount of \$130.00.
- ☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

DATE: August 24, 2006

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

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DOCKET NO.: CRDS-0068
Application No.: Not yet assigned

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Robert Falotico, et al.

Confirmation No.: Not yet assigned

Application No.: Not yet assigned

Group Art Unit: Not yet assigned

Filing Date: August 24, 2006

Examiner: Not yet assigned

For: **Drug/Drug Delivery Systems for the Prevention and Treatment of Vascular Disease**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

**DECLARATION BY ATTORNEY IN SUPPORT OF PETITION TO MAKE SPECIAL
BECAUSE OF ACTUAL INFRINGEMENT (MPEP § 708.02)**

I, S. Maurice Valla, Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia PA, 19103, Registration No. 43,966, Telephone No. 215-564-3100, am the attorney of record for Applicants and make the following declarations.

1. Claims 1 to 14 are presently pending. Claim 1 is directed to a drug delivery device comprising an intraluminal stent, a nonerodible polymeric coating affixed to the stent, and a dose of from about 64 µg to about 197 µg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating. The claim further recites that the device releases a portion of the dose on any of days three to about fifty-six following intraluminal implantation. Independent claim 8 is similar to claim 1, but recites that the rapamycin or macrocyclic triene analog thereof is present at a dose of from about 2 µg to about 30 µg per millimeter of stent length. Dependent claims 3 and 10 specify that the devices release a portion

DOCKET NO.: CRDS-0068**PATENT****Application No.:** Not yet assigned

of the dose during a period of about two weeks to about six weeks following intraluminal implantation. Claim 5 recites a device according to claim 1 or 3 that contains from about 64 μg to about 125 μg of the drug. Claim 12 recites a device according to claim 8 or 10 wherein the rapamycin or macrocyclic triene analog thereof is present at a dose of from about 3 μg to about 13 μg per millimeter of stent length. Claims 6, 7, 13 and 14 are directed to methods of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting a drug delivery device as defined above in the lumen of said coronary artery.

2. Attached as exhibits hereto are press releases issued by Guidant Corporation ("Guidant") describing certain of its activities relating to drug eluting stents. In a release dated January 30, 2006 (Exhibit 1), Guidant announced that it has received Conformité Européenne (CE) Mark Approval for its XIENCE™ V Everolimus Eluting Coronary Stent System. In the same press release, Guidant states that it "is ramping up manufacturing and building inventory to supply ongoing clinical trials and to support the European launch of XIENCE™ V beginning in the second quarter of 2006."

3. In a release dated October 19, 2005 (Exhibit 2), Guidant announced that inspection of its manufacturing facilities in Temecula, California had been successfully concluded as part of its submission for CE Mark approval to market the XIENCE™ V Everolimus Eluting Coronary Stent System in Europe. Guidant reported that its European Notified Body found no nonconformities and would recommend certification for Guidant's manufacturing facility for XIENCE™ V.

4. Since Guidant's approved manufacturing facility for XIENCE™ V is in Temecula, California, I conclude that the "ramping up manufacturing and building inventory to . . . support the European launch of XIENCE™ V" to which Guidant's January 30, 2006, release refers is being performed in the United States. Thus, on the basis of these public statements by Guidant, I conclude that Guidant is "making" XIENCE™ V and building inventory in the United States to support launch of the product in Europe.

DOCKET NO.: CRDS-0068

PATENT

Application No.: Not yet assigned

5. Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

6. I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases and other publicly available documents, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of at least claims 1, 3, 5, 6 to 8, 10, and 12 to 14 on file in this application.

7. Everolimus is a macrocyclic triene analog of rapamycin, bearing a stable 2-hydroxyethyl chain substitution at position 40 on the rapamycin structure (Exhibits 5,6). An article published in EuroIntervention in 2005 (Exhibit 7) confirms that everolimus binds with FKBP12 (*see* page 59, col. 1), and that the XIENCE™ V product is intended for use in method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty (*see e.g.*, page 59, col. 1). This article further confirms that XIENCE™ V product comprises a MULTI-LINK VISION® stent bearing a coating that comprises a nonerodible polymer blended with everolimus at a dose of 100 µg per cm² (*see* page 59, col. 2). On the basis of this information, I conclude that the XIENCE™ V product comprises an intraluminal stent, a nonerodible polymeric coating affixed to the stent, and rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the coating at a dose of 100 µg per cm².

8. Attached hereto is the Declaration of Ramesh V. Marrey, Ph.D., an engineer at Cordis Corporation with considerable familiarity with intraluminal stents (Exhibit 8). Dr. Marrey performed surface area measurements on two MULTI-LINK VISION® stents of a size (*i.e.*, 3.0 mm X 18 mm) that is commonly used in percutaneous transluminal coronary angioplasty (*Id.*, ¶2). From these measurements, Dr. Marrey calculates the surface area of this size MULTI-LINK VISION® stent to be approximately 0.92 cm² (*Id.*, ¶8). Since the XIENCE™ V product is a MULTI-LINK VISION® stent that is said to bear a coating comprising 100 µg per cm² of everolimus, each 3.0 mm X 18 mm XIENCE™ V product would be expected to include approximately 92 µg total of everolimus (*i.e.*, 100 µg per cm² multiplied by 0.92 cm²), or approximately 5.1 µg of everolimus per millimeter of stent length.

DOCKET NO.: CRDS-0068

PATENT

Application No.: Not yet assigned

9. It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of at least claims 1, 3, 5, 6 to 8, 10, and 12 to 14 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

10. I have a knowledge of the pertinent prior art by virtue of the prosecution histories of the parents of the instant application and other patents owned by the assignee of the instant application. All such material art is provided to the Examiner as

☐ having been filed

☒ being filed

in a respective Information Disclosure Statement.

11. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATE: August 24, 2006

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

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One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

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Exhibit X

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

JOHNSON & JOHNSON, a New Jersey
Corporation,

Plaintiffs,

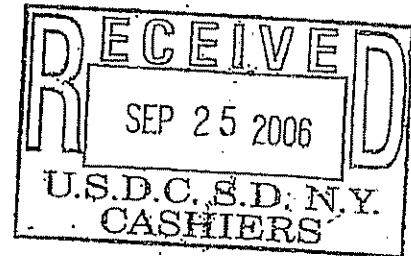
- against -

GUIDANT CORPORATION, an Indiana
Corporation, BOSTON SCIENTIFIC
CORPORATION, a Delaware Corporation, and
ABBOTT LABORATORIES, an Illinois
Corporation,

Defendants.

JUDGE LYNCH
06 CV 7685
Civil Action No. _____

Complaint



Johnson & Johnson ("J&J"), by its attorneys, Kramer Levin Naftalis & Frankel
LLP, for its complaint against Guidant Corporation ("Guidant"), Boston Scientific Corporation
("Boston Scientific") and Abbott Laboratories ("Abbott"), alleges as follows:

I. Nature of the Action

1. This action arises out of the highly publicized takeover battle between J&J
and Boston Scientific to acquire Guidant. While Boston Scientific ultimately succeeded in its
takeover bid for Guidant, it did so only because Guidant leaked confidential information to a
third party, Abbott, for the purpose of arranging a prepackaged divestiture of significant Guidant
businesses to Abbott. Based on these disclosures, which were in material breach of the terms of
Guidant's merger agreement with J&J, Abbott agreed to enter into a divestiture and financing
agreement with Boston Scientific, which allowed Boston Scientific to make an offer for Guidant
that would not require a lengthy and uncertain antitrust review. This, in turn, allowed Guidant to
accept Boston Scientific's offer as "superior" to J&J's offer and to terminate the agreement with

J&J. Thus, Guidant's breach of its agreement with J&J, and Boston Scientific's and Abbott's tortious interference with that agreement, deprived J&J of the benefit of the bargain of its merger with Guidant and caused it to suffer damages.

2. In December 2004, J&J and Guidant entered into a merger agreement that provided that J&J would pay \$25.4 billion to acquire Guidant, or \$76 per Guidant share (the "Initial Merger Agreement"). Guidant's shareholders approved the merger. The price was subsequently changed to \$21.5 billion, or \$63.08 per share, as a result of various product recalls and legal problems that surfaced at Guidant. In this regard, the parties entered into an Amended and Restated Agreement and Plan of Merger dated November 14, 2005 (the "Merger Agreement").

3. Like any large multi-national acquisition, the merger was subject to antitrust approval by U.S., European Union and other foreign regulators. Over the following ten months, J&J reached an agreement with domestic and foreign regulators which, among other things, would grant a non-exclusive license for certain patents to Abbott to facilitate antitrust approval for the merger with Guidant.

4. Pending the closing of the merger, Guidant was prohibited under the express terms of the Merger Agreement from soliciting alternative offers and had limited ability to respond to an unsolicited bid from another party. Under the "No Solicitation" provision in the Merger Agreement — which was designed to prevent Guidant from using the Merger Agreement to solicit higher offers — Guidant was prohibited from providing confidential business information to any company, or its representatives, unless that company was making an unsolicited "Takeover Proposal" (*i.e.*, a proposal to acquire 15% or more of Guidant) under

terms that were likely to result in a bid that constituted a "Superior Proposal" to the merger with J&J. Guidant also could not facilitate or cooperate with a Takeover Proposal other than through discussions with, and disclosures to, the person making such a Takeover Proposal. Under no circumstances could Guidant provide confidential business information to or discuss or negotiate with any third party that was not making a bona fide Takeover Proposal.

5. In December 2005, just as the J&J/Guidant merger was about to close, Boston Scientific made a bid to acquire Guidant for \$25 billion, or \$72 per Guidant share. While nominally higher in price than the renegotiated deal with J&J, Boston Scientific's offer was fraught with uncertainty and timing issues that rendered its proposal patently inferior to the merger with J&J. For example, unlike J&J, which had spent much of the past year resolving potential antitrust issues by entering into a License Agreement with Abbott and a Consent Decree with the regulators, Boston Scientific had not even begun the pre-merger notification process, much less resolved its own antitrust issues, at the time of its announced bid.

6. After receiving a Takeover Proposal from Boston Scientific, Guidant's management allowed Boston Scientific to perform limited due diligence. What Guidant did not disclose until after the fact, however, was that it simultaneously allowed Abbott — a third party with absolutely no right to receive any confidential information from Guidant under the No Solicitation provision and which had already agreed to facilitate J&J's bid — an even "deeper dive" into Guidant's confidential business information to determine whether Abbott would now be willing to enter into a pre-packaged divestiture agreement with Boston Scientific to clear any antitrust hurdles. In so doing, Guidant materially breached the No Solicitation provision of its Merger Agreement with J&J.

7. Based on the information disclosed to it by Guidant, Abbott and Boston Scientific entered into an agreement to divest Guidant's entire vascular intervention ("VI") business and other assets and Boston Scientific then made a formal proposal to acquire Guidant for \$72 per share. On January 25, 2006, after several counter-proposals from J&J and Boston Scientific, Guidant announced that it was terminating the Merger Agreement with J&J and entering into an acquisition agreement with Boston Scientific for \$27 billion.

8. Abbott would not have agreed to a pre-packaged divestiture without the confidential information it received in violation of the "No-Solicitation" provision of J&J's Merger Agreement with Guidant. Without a pre-packaged divestiture agreement, Boston Scientific could not have made a proposal that would have been acceptable to Guidant's Board of Directors or shareholders, both because it would have been conditioned on reaching an agreement with Abbott or some other party to resolve antitrust issues and would have entailed a lengthy antitrust review, the outcome of which would have been uncertain.

9. Guidant could have terminated its Merger Agreement with J&J and then provided information to Abbott, but would then have lost the ability to keep J&J bound to a deal if a transaction with Boston Scientific failed to materialize. Guidant was also able to use its agreement with J&J to better its negotiating position with Boston Scientific. By keeping J&J contractually bound while it facilitated what was ultimately declared a Superior Proposal from Boston Scientific, Guidant acted in bad faith and in violation of its contractual restrictions pending the closing of the Merger Agreement with J&J.

10. Boston Scientific and Abbott were well aware that Guidant had entered into the Merger Agreement with J&J; indeed, Abbott had agreed to facilitate consummation of

that transaction before it began dealing with Boston Scientific behind J&J's back. By their actions, these defendants induced Guidant to breach that agreement by disclosing confidential information to Abbott with the goal of ensuring the success of Boston Scientific's Takeover Proposal.

11. As a result of Guidant's willful and material breach, and the tortious interference by Boston Scientific and Abbott, J&J was deprived of the benefit of its merger agreement and suffered damages that it now seeks to recover through this action.

II. Jurisdiction and Venue

12. The Court has diversity jurisdiction over the subject matter of this case, under 28 U.S.C. § 1332, because this case arises among citizens of different states and the amount in controversy exceeds the sum or value of \$75,000.

13. The Court has jurisdiction over the parties, each of which is a corporation doing business in the State of New York, and jurisdiction to grant all the relief requested by J&J.

14. Venue is proper in the Southern District of New York because one party, Guidant, is subject to and has consented to the jurisdiction of this Court and there is no other district in which this action may otherwise be brought.

III. The Parties

15. J&J is a New Jersey corporation with its headquarters and principal place of business at One Johnson & Johnson Plaza, New Brunswick, New Jersey. Through its operating subsidiaries, J&J is a multi-national manufacturer and distributor of health care, surgical, biotechnology, and personal hygiene products, as well as a provider of related services

for the consumer, pharmaceutical, medical devices, and diagnostics markets. J&J has more than 230 operating companies, which employ approximately 116,000 people in 57 countries and sell products in the United States and around the world.

16. Guidant is an Indiana corporation having a principal place of business at 11 Monument Circle, Indianapolis, Indiana. It is now a wholly-owned subsidiary of Boston Scientific. Guidant designs, develops, and markets cardiovascular medical products, including pacemakers and implantable defibrillators.

17. Boston Scientific is a Delaware corporation having a principal place of business at One Boston Scientific Place, Natick, Massachusetts. Boston Scientific develops, manufactures and markets a range of medical devices and procedures.

18. Abbott is an Illinois corporation having a principal place of business at 100 Abbott Park Road, Abbott Park, Illinois. Abbott develops, manufactures, and markets pharmaceutical and nutritional products, as well as surgical and diagnostic devices.

IV. Background Facts

(a) J&J and Guidant Engage in Confidential Merger Discussions

19. Among other products, J&J, through its subsidiary Cordis Corporation ("Cordis"), markets medical devices for the treatment of cardiovascular disorders, including a coronary stent known as the Cypher stent. A stent is a metallic device surgically inserted to keep arteries open after balloon angioplasty to clear blockages. The Cypher stent provides a mechanical scaffold to keep the vessel open while a drug is slowly released from the stent to

prevent the build-up of new tissue that re-clogs the artery. Stents that work with drugs like this are known in the industry as drug-eluting stents ("DES").

20. DES account for over 80% of the U.S. coronary stent market. Aside from Cordis, Boston Scientific is the only other company that markets DES in the U.S., with Cordis having approximately a 45% market share and Boston Scientific approximately a 55% market share. Guidant, Abbott and another company called Medtronic are all in the process of seeking, or undertaking the preparations necessary to seek, approval of the Food and Drug Administration to market DES in this country.

21. During the fall 2004, J&J engaged in discussions with Guidant about the possibility of entering into a business transaction whereby J&J would acquire Guidant. The acquisition of Guidant represented an opportunity for J&J to expand its business into the cardiac rhythm management market for implantable pacemakers and defibrillators.

22. On or about August 4, 2004, J&J and Guidant entered into a Confidentiality Agreement that provided that information exchanged between J&J and Guidant would be used solely for the purpose of exploring a possible negotiated business arrangement and not for any other business or competitive purpose.

(b) J&J and Guidant Enter into a Merger Agreement

23. On December 15, 2004, J&J and Guidant entered into the Initial Merger Agreement pursuant to which J&J agreed to pay \$25.4 billion in cash and stock or \$76 per share to acquire Guidant. The closing of the merger was conditioned on (i) approval of the deal by Guidant shareholders, (ii) approval for listing on the New York Stock Exchange of newly registered J&J stock for issuance to Guidant shareholders, (iii) regulatory approval of the

transaction, including any divestitures, from U.S. and European Commission antitrust authorities, and (iv) the accuracy of the representations and warranties set forth in the agreement.

24. With Guidant's assistance, J&J prepared and filed with the Securities and Exchange Commission a Registration Statement on Form S-4 in connection with the issuance of J&J stock in the merger, as well as a Proxy Statement for the Merger that was included as a Prospectus.

25. Guidant gave notice of, convened, and held a meeting of its shareholders solely for the purpose of obtaining shareholder approval of the merger. On or about April 27, 2005, Guidant shareholders approved the merger.

26. J&J also sought the necessary antitrust clearance for the merger in the United States, Europe, and Canada. To this end, J&J filed a pre-merger notification under the Hart-Scott-Rodino Antitrust Act of 1976 with the Federal Trade Commission ("FTC") on January 18, 2005.

27. In discussions with the FTC, the agency objected to the proposed transaction on the ground that a merger between one of two actual competitors in the DES market with one of the three potential competitors would lessen competition in that market. On August 12, 2005, J&J and Abbott entered into a License Agreement whereby J&J granted Abbott a non-exclusive license to certain patents in the DES field in the event the transaction was consummated in order to increase the likelihood that Abbott would successfully enter the DES market. After lengthy negotiations, and based in part on the agreement between J&J and Abbott, the FTC and J&J entered into a Consent Order on November 2, 2005 to resolve the FTC's antitrust concerns.

28. In the meantime, numerous regulatory and legal problems surfaced involving Guidant products being recalled, lawsuits against Guidant being filed, and Guidant being investigated by the New York Attorney General. On October 18, 2005, J&J announced that the company was considering alternatives to its proposed acquisition of Guidant and on November 7, Guidant sued J&J claiming a breach of the Initial Merger Agreement. On November 14, Guidant accepted a revised offer of \$21.5 billion, or \$63.08 per Guidant share, the Merger Agreement was executed and the lawsuit was discontinued.

(c) The Merger Agreement Contained Strict Limitations on Guidant's Ability to Solicit or Cooperate with Competing Bids, Designed to Protect the Benefit of J&J's Bargain

29. Pursuant to the Merger Agreement, Guidant was prohibited from either (i) soliciting, initiating or knowingly encouraging, or taking any other action designed to, or which could reasonably be expected to, facilitate, any competing proposal to acquire Guidant or (ii) entering into, continuing or otherwise participating in any discussions or negotiations regarding, or furnishing to any person any information, or otherwise cooperating with any such proposal. These restrictions were designed to prevent Guidant from using the J&J offer as a means of obtaining higher bids for the company.

30. In particular, Section 4.02 of the Merger Agreement, titled "No Solicitation," provided as follows:

The Company [i.e., Guidant] shall not, nor shall it authorize or permit any of its Subsidiaries or any of their respective directors, officers or employees or any investment banker, financial advisor, attorney, accountant or other advisor, agent or representative (collectively, "Representatives") retained by it or any of its Subsidiaries to, directly or indirectly through another person, (i) solicit, initiate or knowingly encourage, or take any other action designed to, or which could reasonably be expected to, facilitate, any Takeover Proposal or (ii) enter into, continue or otherwise

participate in any discussions or negotiations regarding, or furnish to any person any information, or otherwise cooperate in any way with, any Takeover Proposal. (Emphasis added).

31. Section 4.02 of the Merger Agreement defined a "Takeover Proposal" as basically a bid for at least 15% of Guidant's assets or businesses:

The term "Takeover Proposal" means any inquiry, proposal or offer from any person relating to, or that could reasonably be expected to lead to, any direct or indirect acquisition or purchase, in one transaction or a series of transactions, of assets (including equity securities of any Subsidiary of the Company) or businesses that constitute 15% or more of the revenues, net income or assets of the Company and its Subsidiaries, taken as a whole, or 15% or more of any class of equity securities of the Company, any tender offer or exchange offer that if consummated would result in any person beneficially owning 15% or more of any class of equity securities of the Company, or any merger, consolidation, business combination, recapitalization, liquidation, dissolution, joint venture, binding share exchange or similar transaction involving the Company or any of its Subsidiaries pursuant to which any person or the shareholders of any person would own 15% or more of any class of equity securities of the Company or of any resulting parent company of the Company, in each case other than the transactions contemplated by this Agreement.

32. Notwithstanding these provisions, and in order to allow Guidant's directors to meet their fiduciary obligations to Guidant's shareholders, the Merger Agreement provided that if Guidant's Board of Directors, in consultation with outside legal counsel and a qualified financial advisor, determined that an unsolicited Takeover Proposal constituted or was reasonably likely to lead to a "Superior Proposal," as defined below, then, and only then, Guidant could (i) provide information to the "person making such Takeover Proposal (and its Representatives)," pursuant to an appropriate confidentiality agreement and as long as Guidant simultaneously provided (or already had provided) the information to J&J, and/or (ii) "participate in discussions or negotiations with the person making such Takeover Proposal (and its Representatives)."

33. In this regard, Section 4.02 provided as follows:

Notwithstanding the foregoing, at any time prior to obtaining the Shareholder Approval, in response to a bona fide written Takeover Proposal that the Board of Directors of the Company reasonably determines (after consultation with outside counsel and a financial advisor of nationally recognized reputation) constitutes or is reasonably likely to lead to a Superior Proposal, and which Takeover Proposal was not solicited after the date hereof and was made after the date hereof and did not otherwise result from a breach of this Section 4.02(a), the Company may, subject to compliance with Section 4.02(c), (x) furnish information with respect to the Company and its Subsidiaries to the person making such Takeover Proposal (and its Representatives) pursuant to a customary confidentiality agreement not less restrictive to such person than the confidentiality provisions of the Confidentiality Agreement, *provided* that all such information has previously been provided to Parent or is provided to Parent prior to or substantially concurrent with the time it is provided to such person, and (y) participate in discussions or negotiations with the person making such Takeover Proposal (and its Representatives) regarding such Takeover Proposal.

34. As further defined in Section 4.02, "Representatives" of a person making a Takeover Proposal included only that person's "Subsidiaries or any of their respective directors, officers or employees or any investment banker, financial advisor, attorney, accountant or other advisor, agent or representative (collectively, 'Representatives')." Guidant was expressly prohibited from giving information to, or participating in discussions with, any other persons.

35. Whether a Takeover Proposal constituted or likely would lead to a Superior Proposal was to be based not only on its financial terms, but also on whether it was "reasonably capable of being completed, taking into account all financial, legal, regulatory and other aspects of such proposal." Thus, under Section 4.02:

The term "Superior Proposal" means any bona fide offer made by a third party that if consummated would result in such person (or its shareholders) owning, directly or indirectly, more than 80% of

the shares of Company Common Stock then outstanding (or of the shares of the surviving entity in a merger or the direct or indirect parent of the surviving entity in a merger) or all or substantially all the assets of the Company, which the Board of Directors of the Company reasonably determines (after consultation with a financial advisor of nationally recognized reputation) to be (i) more favorable to the shareholders of the Company from a financial point of view than the Merger (taking into account all the terms and conditions of such proposal and this Agreement (including any changes to the financial terms of this Agreement proposed by Parent in response to such offer or otherwise)) and (ii) *reasonably capable of being completed, taking into account all financial, legal, regulatory and other aspects of such proposal.* [Emphasis added]

36. In sum, under the Merger Agreement, Guidant could not solicit any Takeover Proposal from another person. In the event that it received an unsolicited Takeover Proposal, which it determined upon consultation with its legal and financial advisors was or could become a Superior Proposal, Guidant could furnish information to, and conduct discussions with, only the person (or its Representatives) making such a Takeover Proposal.

37. The Merger Agreement also provided that in the event Guidant's Board received a Superior Offer, Guidant was required to notify J&J of the terms of that offer and give J&J five business days to make a competing offer, which Guidant would be required to consider before it could terminate the Merger Agreement without a breach.

(d) Boston Scientific Makes a Last-Minute Bid, and Guidant Breaches the Merger Agreement to Facilitate Turning It into a Superior Proposal

38. On December 5, 2005, before the merger between J&J and Guidant had closed, Boston Scientific announced a bid for Guidant, offering \$25 billion, or \$72 per share. While nominally higher in price than the J&J deal, Boston Scientific's offer was contingent upon, among other things, receiving regulatory approval and was therefore subject to uncertainty and delay.

39. On January 8, 2006, Boston Scientific submitted a formal proposal to acquire Guidant for \$72 per share. As part of this formal offer, Boston Scientific also announced that it had entered into an agreement with Abbott to divest Guidant's VI and endovascular businesses to Abbott, as well as to share rights to Guidant's DES program, in order to facilitate prompt antitrust review and approval. Abbott also agreed to provide a \$700 million loan to Boston Scientific.

40. Based on statements made in a January 9, 2006 conference call with analysts to discuss the Boston Scientific proposal, it became clear that Guidant had cooperated with and facilitated Boston Scientific's Takeover Proposal by impermissibly providing confidential information to Abbott. This in turn enabled Boston Scientific to enter into the agreement with Abbott, which was critical to Boston Scientific's ability to have its offer declared by Guidant as a Superior Proposal and thereby have it accepted in lieu of the J&J transaction.

41. On the conference call, Larry Best, Chief Financial Officer for Boston Scientific, emphasized the importance of the agreement with Abbott to Boston Scientific's Takeover Proposal. In Mr. Best's words, the Abbott agreement was "critically important not only for the quick completion of the Guidant acquisition but also for the business prospects of the combined company." Mr. Best explained: "As we said when we announced our initial proposal our intention was to divest Guidant's vascular intervention and endovascular business in an effort to obtain rapid antitrust approval for the Guidant acquisition. Therefore, we have executed a binding agreement with Abbott. Abbott will buy Guidant's VI and endovascular businesses when we complete this transaction with Guidant."

42. During the Q&A session at the end of the call, one analyst asked Boston Scientific's Chief Operating Officer, Paul LaViolette, whether Boston Scientific had "seen part of the [Guidant DES] data as a part of your due diligence and if not, is there some contingency that exists for Abbott should the [Guidant DES] data prove disappointing . . . ?"

43. Electing to respond to this question himself, Mr. Best was quoted as saying:

Let me explain the due diligence process. As you can imagine, Guidant, you know was very protective of their program in terms of our doing due diligence. *We had the opportunity to do a certain level of due diligence. Abbott had the opportunity to do a much deeper dive on due diligence.* My understanding from their due diligence is that they were very impressed with the data and what they found, and that is how they came up with the valuation and the decision to move forward. (Emphasis added).

44. Thus, at some point in time between Boston Scientific's announcement of its bid for Guidant on December 5, 2005, and Boston Scientific's submission of a formal proposal on January 8, 2006, Guidant not only allowed Boston Scientific to conduct due diligence on its businesses but also disclosed even more confidential business information to Abbott — which had no independent right to receive any information and was prohibited from receiving any information under the Merger Agreement — about its VI and endovascular businesses.

45. As a result of the "deeper dive" it was permitted into Guidant's confidential business information, Abbott was able to make a "decision to move forward" and agree to acquire the entire VI business and other assets that Boston Scientific needed to divest to expedite antitrust regulatory approval of its proposed acquisition of Guidant. Without these

agreements, Boston Scientific's Takeover Proposal would not have been viable, much less superior to J&J's.

(e) Guidant's Impermissible Disclosures Constituted a Willful and Material Breach of the Merger Agreement

46. Immediately upon learning that Guidant had divulged confidential business information to Abbott, in breach of the No Solicitation provision of the Merger Agreement, J&J's General Counsel raised the issue with Guidant's General Counsel. In a follow-up letter dated January 23, 2006, J&J's General Counsel wrote to Guidant noting the apparent breach of Section 4.02 of their Merger Agreement and demanding an explanation. In response, Guidant's General Counsel attempted to justify Guidant's actions by, among other things, claiming that "Boston Scientific brought Abbott into the transaction as part of Boston Scientific's 'Takeover Proposal'" and that Abbott was a "joint bidder" for Guidant along with Boston Scientific. The matter remained unresolved.

47. Abbott was not a "joint-bidder" for Guidant. Abbott did not make a Takeover Proposal either on its own or in conjunction with Boston Scientific and, therefore, was not entitled to receive any confidential information from Guidant. Nor was Abbott a "Representative" of Boston Scientific, as that term is defined in Section 4.02 of the Merger Agreement. Rather, at all times Abbott was a third party divestiture candidate dealing at arms' length with Boston Scientific in negotiating the acquisition of certain businesses that would be divested in the event that Boston Scientific's Takeover Proposal was accepted.

48. As Boston Scientific itself noted during the January 9 conference call, an executed agreement with Abbott was critically important both to rapid antitrust approval of a potential acquisition by Boston Scientific and to the perceived business prospects of the

combined company. Just as J&J entered into a Licensing Agreement with Abbott in anticipation of closing its Merger Agreement with Guidant, Boston Scientific needed to enter into a much more extensive agreement with Abbott — divesting entire businesses — to ease antitrust approval of its own otherwise inferior proposal to acquire Guidant. By leaking confidential information to Abbott, a third-party divestiture candidate, Guidant, in violation of the No Solicitation restrictions in its Merger Agreement with J&J, thus knowingly and willfully facilitated Boston Scientific's Takeover Proposal becoming a Superior Proposal.

(f) Guidant Deems Boston Scientific's Offer to be a "Superior Proposal"

49. On January 10, 2006, Guidant's Board of Directors met to consider whether Boston Scientific's offer was a "Superior Proposal."

50. Faced with the prospect of losing the transaction that it had pursued for more than a year, J&J chose to reconsider the amount it was willing to offer for Guidant. On January 11, J&J and Guidant announced a revised Merger Agreement, raising the price to \$68.06 per Guidant share. On the next day, however, Boston Scientific improved its own offer to \$73 per Guidant share. The following day, January 13, 2006, J&J and Guidant announced a further revision to their Merger Agreement, raising the acquisition price to \$71 per share, but once again, on January 17, 2006, Boston Scientific raised its offer, this time to \$80 per share.

51. Later in the day on January 17, 2006, Guidant's Board announced that Boston's bid was deemed a "Superior Proposal" to the existing deal with J&J. On January 25, 2006, Guidant announced that it was terminating the Merger Agreement with J&J, as it was entitled to do upon determining that there was a Superior Proposal, and entering into an acquisition agreement with Boston Scientific for \$27 billion. J&J ultimately received a \$705

million "termination fee" under the terms of its Merger Agreement. However, as the Merger Agreement itself makes clear, "no such termination shall relieve any party hereto from any liability or damages resulting from the willful and material breach by a party of any of its representations, warranties, covenants or agreements set forth in this Agreement." (Merger Agreement at § 7.02).

52. As a result of Guidant's willful and material breach of the No Solicitation provision of the Merger Agreement, which facilitated Boston Scientific's Takeover Proposal through the prohibited confidential disclosures to third-party divestiture candidate Abbott, J&J was wrongfully deprived of the full benefits of its bargain and suffered damages that it now seeks to recover.

V. Claims for Relief

First Cause of Action
for Breach of Contract
(Against Defendant Guidant)

53. J&J repeats and realleges the allegations of paragraphs 1 to 52.

54. J&J entered into a valid, binding contract embodied in the Merger Agreement. A material term of the Merger Agreement was a "No Solicitation" clause, as set forth in Section 4.02 of the Merger Agreement. The No Solicitation clause was designed to protect the terms of the bargain that the parties struck, pending the closing of their transaction, while providing Guidant with the limited ability to receive and negotiate unsolicited alternative proposals.

55. Assuming that Boston Scientific's December 5, 2005 bid could be viewed as reasonably likely to lead to a Superior Proposal, Guidant was only permitted to provide confidential information to Boston Scientific and its Representatives, as defined in the Merger Agreement. Since Abbott was neither a person making a Takeover Proposal nor a Representative of Boston Scientific, but only a third-party divestiture candidate, permitting Abbott to take a "deeper dive" into Guidant's confidential information was a clear breach of the Merger Agreement.

56. This breach went to the heart of J&J's bargain, facilitating a competing bid by providing confidential information to a person not entitled to receive such information under the No Solicitation clause.

57. The breach was also material and harmed J&J. Had Abbott not been provided with Guidant's confidential business information, Abbott would not have been able to enter into the divestiture agreement, which in turn facilitated and enabled Boston Scientific's Takeover Proposal to be viewed as a Superior Proposal.

58. As a result of Guidant's willful and material breach, J&J was deprived of the benefit of its bargain under the Merger Agreement and suffered damages.

59. J&J made reasonable and diligent attempts to mitigate its damages.

Second Cause of Action
for Breach of the Implied Duty of Good Faith and Fair Dealing
(Against Defendant Guidant)

60. J&J repeats and realleges the allegations of paragraphs 1 to 52.

61. As a matter of common law, as well as the law of the State of Indiana, every contract imposes on the parties thereto an implied duty of good faith and fair dealing.

62. Defendant Guidant breached the implied duty of good faith and fair dealing by negotiating and facilitating a competing Takeover Proposal from another party, Boston Scientific, during the time that it was party to a binding Merger Agreement with J&J, in violation of the Merger Agreement.

63. Guidant could have terminated the Merger Agreement with J&J, paid the termination fee, and assumed the risk of being able to negotiate and enter into an alternative deal with Boston Scientific, subject to the uncertainty of being able to consummate a divestiture and the inevitable delay and uncertainty of antitrust regulatory review. Instead, Guidant surreptitiously facilitated an alternative proposal with Boston Scientific, through the prohibited disclosure of confidential information to Abbott, a third party divestiture candidate. Guidant thus used the Merger Agreement to negotiate a better offer in breach of its implied duty of good faith and fair dealing.

64. As a result of Guidant's breach of the implied duty of good faith and fair dealing, J&J was deprived of the benefit of its bargain under the Merger Agreement and suffered damages.

Third Cause of Action
For Tortious Interference with Contract
(Against Defendants Boston Scientific and Abbott)

65. J&J repeats and realleges herein the allegations of paragraphs 1 to 52.

66. Boston Scientific and Abbott were aware that J&J had entered into a binding Merger Agreement with Guidant and were aware that the Merger Agreement prohibited the disclosure of confidential information to third parties.

67. Boston Scientific and Abbott intentionally induced Guidant to breach the Merger Agreement with J&J by disclosing confidential business information to Abbott.

68. Boston Scientific and Abbott thus knowingly, intentionally, and maliciously interfered with J&J's binding contract to acquire Guidant under the terms of the Merger Agreement that was on the verge of closing.

69. Abbott emerged from its prohibited due diligence review with a clear picture of Guidant's businesses that enabled it to proceed expeditiously with a divestiture agreement, which in turn facilitated Boston Scientific's ability to make a "Superior Proposal" to Guidant.

70. As a result of Guidant's breaches and Boston Scientific's and Abbott's tortious interference with J&J's Merger Agreement and prospective business opportunity, J&J was damaged.

Prayer for Relief

Wherefore, Plaintiff J&J respectfully requests the following relief:

- (i) that the Court find that Guidant willfully and materially breached the Merger Agreement with J&J;

- (ii) that the Court find that Guidant breached the implied obligation of good faith and fair dealing; and
- (iii) that the Court find that Boston Scientific and Abbott knowingly, intentionally and tortiously interfered with, and induced Guidant to breach, the Merger Agreement;
- (iv) that after making such determinations, the Court award Plaintiff appropriate legal damages (general and special), in an amount to be determined at trial, but in no event less than \$5.5 billion; and
- (v) that the Court award such other necessary and proper relief, including, without limitation, attorneys' fees, interest, costs, as the Court may deem just and proper.

Dated: New York, New York
September 25, 2006

Kramer Levin Naftalis & Frankel LLP

By: 

Harold P. Weinberger (HW3240)
Timothy J. Helwick (TH5833)

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Attorneys for Plaintiff Johnson & Johnson

EXHIBIT 2

IN THE UNITED STATES DISTRICT COURT FOR THE
DISTRICT OF DELAWARE

ABBOTT LABORATORIES and
~~ADVANCED ABBOTT~~
CARDIOVASCULAR SYSTEMS, INC.,

Plaintiffs,

v.

JOHNSON AND JOHNSON, INC. and
CORDIS CORPORATION,

Defendants.

Civil Action No. 06-613-SLR

JURY TRIAL DEMANDED

**SUPPLEMENTAL AND AMENDED COMPLAINT FOR DECLARATORY
JUDGMENT OF PATENT INVALIDITY AND NON-INFRINGEMENT**

Plaintiffs Abbott Laboratories and ~~Advanced Abbott~~ Cardiovascular Systems, Inc. (collectively "Abbott") bring this Supplemental and Amended Complaint against Defendants Johnson and Johnson, Inc. and Cordis Corporation (collectively "J&J"). This is an action for a declaratory judgment and injunctive relief that United States Patent No. 6,585,764 entitled "Stent With Therapeutically Active Dosage Of Rapamycin Coated Thereon" (the "Wright '764 patent"), United States Patent No. 6,808,536 entitled "Stent Containing Rapamycin Or Its Analogs Using A Modified Stent" (the "Wright '536 patent"), ~~and~~ United States Patent No. 6,776,796 entitled "Antiinflammatory Drug and Delivery Device" (the "Falotico '796 patent"), United States Patent No. 7,217,286 entitled "Local Delivery of Rapamycin for Treatment of Proliferative Sequelae Associated with PTCA Procedures. Including Delivery Using a Modified Stent" (the "Wright '7286 patent"), and United States Patent No. 7,223,286 entitled "Local Delivery Of Rapamycin For Treatment Of Proliferative Sequelae Associated With PTCA Procedures. Including Delivery

Using A Modified Stent” (the “Wright ’3286 patent”) are invalid and not infringed by Abbott. The Wright ’764 patent, the Wright ’536 patent, ~~and the Falotico ’796 patent, and the Wright ’7286 patent~~ are attached as Exhibits A – ~~C~~D, respectively. The Issue Notification for the Wright ’3286 patent and the Wright ’3286 patent are attached as Exhibit E. Abbott alleges as follows:

THE PARTIES

1. Abbott Laboratories is a corporation organized under the laws of the State of Illinois and has a principal place of business at 100 Abbott Park Road, North Chicago, Illinois.

2. ~~Advanced~~Abbott Cardiovascular Systems, Inc. (“ACS”), ~~formerly Advanced Cardiovascular Systems, Inc.~~ is a corporation organized under the laws of the State of California and has a principal place of business at 3200 Lakeside Drive, Santa Clara, California. ACS is a subsidiary of Abbott Laboratories.

3. On information and belief, Johnson and Johnson, Inc. is a corporation organized under the laws of the State of New Jersey and has a principal place of business at One Johnson and Johnson Plaza, New Brunswick, New Jersey.

4. On information and belief, Cordis Corporation (“Cordis”) is a corporation organized under the laws of the State of Florida and has a principal place of business in Miami Lakes, Florida. Cordis is a subsidiary of Johnson and Johnson, Inc.

JURISDICTION AND VENUE

5. This action arises under the Patent Laws of the United States (35 U.S.C. § 1 *et seq.*).

6. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

7. This Court has personal jurisdiction, general and specific, over J&J.

8. On information and belief, J&J has systematic and continuous contacts in this judicial district.

9. On information and belief, J&J regularly avails itself of the benefits of this judicial district, including the jurisdiction of the courts.

10. On information and belief, J&J regularly transacts business within this judicial district.

11. On information and belief, J&J regularly sells products in this judicial district. J&J derives substantial revenues from sales in this district.

12. Venue is proper in this district under 28 U.S.C. §§ 1391(b) and (c).

BACKGROUND

13. J&J, and in particular Cordis, directly competes with Abbott in the field of intravascular stents used to treat coronary artery disease.

14. The coronary stent industry is highly litigious. J&J, and in particular Cordis, has a well-known history of suing competitors in this field for patent infringement.

15. On three occasions within the last ten years, Cordis sued ACS in this district, alleging patent infringement involving angioplasty catheters or stents for treating coronary artery disease. (*Cordis Corporation, et al. v. Advanced Cardiovascular Systems, Inc, et al.*, C.A. No. 97-550-SLR; *Cordis Corporation, et al. v. Advanced Cardiovascular Systems, Inc., et al.*, C.A. No. 97-635-SLR; and *Cordis Corporation, et al. v. Advanced Cardiovascular Systems, Inc., et al.*, C.A. No. 98-065-SLR).

16. On three additional occasions within the last ten years, Cordis initiated patent infringement actions in this judicial district involving angioplasty catheters or stents for treating coronary artery disease. (*Cordis Corp. v. Boston Scientific Corp.*, C.A. No. 98-197-SLR; *Cordis*

Corp. v. Medtronic AVE, Inc., C.A. No. 00-886-SLR; and Cordis Corp. v. Boston Scientific Corp., C.A. No. 03-027-SLR).

17. ~~16.~~ In early 2006, J&J and Boston Scientific Corporation ("BSC") each were bidding to acquire assets of Guidant Corporation ("Guidant"), which at the time was the parent corporation of ACS. In conjunction with BSC's bid, ACS would be acquired by Abbott Laboratories, which was the ultimate result.

18. ~~17.~~ One of the key assets of ACS was the XIENCE V drug eluting stent system ("XIENCE V"), which elutes a proprietary drug known as everolimus. ACS holds an exclusive patent license to use everolimus for drug eluting stents. In clinical trials, everolimus has proven superior to other drugs.

19. ~~18.~~ On information and belief, J&J believed in early 2006 that the XIENCE V would be launched within a few months.

J&J's Public Threats To Sue For Patent Infringement By XIENCE V

20. ~~19.~~ On information and belief, J&J undertook a public campaign to cast a cloud over the launch of the XIENCE V.

21. ~~20.~~ On information and belief, as a main thrust of this public campaign, J&J alleged that the XIENCE V would infringe patents allegedly owned by J&J and that J&J would sue Abbott for infringement by the XIENCE V following its launch. On information and belief, J&J's allegations related to at least the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

22. ~~21.~~ On information and belief, J&J broadcasted threatening statements to industry analysts regarding alleged infringement by XIENCE V, for publication in furtherance of J&J's public campaign.

23. ~~22.~~ For example, the Prudential Equity Group, LLC published a report on January 20, 2006, titled "JNJ: Takes Off The Gloves In Its Fight With Boston Scientific For Guidant," attached as Exhibit ~~DE~~ ("the Prudential report"). In the Prudential report, parties are identified by their stock symbols: ABT for Abbott, GDT for Guidant, JNJ for J&J, and BSX for BSC.

24. ~~23.~~ On information and belief, the Prudential report relied on information provided in pertinent part by J&J.

25. ~~24.~~ Among other things, the Prudential report stated:

JNJ claims that 2 of its patents may be infringed if a company tries to launch a drug-eluting stent coated with a rapamycin derivative such as . . . GDT's everolimus. The potential for JNJ to prevent ABT and BSX from marketing the Xience-V DES, could give the GDT board pause for approving a BSX-GDT merger.

* * *

If BSX acquires GDT, BSX would sell GDT's vascular intervention (VI) business, including shared rights to GDT's promising everolimus-coated stent, Xience-V, to ABT. Although JNJ's patents have never been litigated, JNJ believes it has a strong intellectual property (IP) position with regard to the use of rapamycin derivatives on a stent. JNJ could pursue a preliminary injunction if ABT and BSX try to launch an everolimus-coated . . . stent. . . . According to JNJ, the key patents are the Falotico (6,776,796) and Wright (6,585,764) patents.

26. ~~25.~~ On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Prudential analysts.

27. ~~26.~~—On January 23, 2006, A.G. Edwards & Sons, Inc. published a report titled “Healthcare Industry Note: The Game May Be Far From Over,” attached as Exhibit ~~E~~G (“the AG Edwards report”).

28. ~~27.~~—On information and belief, the AG Edwards report relied on information provided in pertinent part by J&J.

29. ~~28.~~—Among other things, the AG Edwards report stated:

We have had conversations with Johnson & Johnson (JNJ) and Boston Scientific (BSX) and others recently that lead us to believe that the Guidant (GDT) game is far from over.

* * *

We were also reminded by JNJ that it had three patents related to ‘-limus’ compounds that it thought precluded any other company from using such a compound on a stent. We were only given two patent numbers (6776796 [the Falotico ’796 patent] and 6585764 [the Wright ’764 patent])

30. ~~29.~~—On information and belief, the third patent referenced in J&J’s threatening statements was the Wright ’536 patent.

31. ~~30.~~—On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to AG Edwards analysts.

32. On January 13, 2006, Citigroup published a report titled “An INTERESTing New Offer,” attached as Exhibit H (“the January 13, 2006 Citigroup report”).

33. On information and belief, the January 13, 2006 Citigroup report relied on information provided in pertinent part by J&J.

34. Among other things, the January 13, 2006 Citigroup report stated:

The [Wright and Falotico] patents have never been challenged or enforced because no other company has launched a limus-based drug-eluting stent in the US, but are likely to eventually lead to litigation.

35. Citigroup published an additional report on March 23, 2006 titled "Deconstructing Xience," attached as Exhibit I ("the March 23, 2006 Citigroup report"). In the March 23, 2006 Citigroup report J&J is identified by its stock symbol JNJ.

36. On information and belief, the March 23, 2006 Citigroup report relied on information provided in pertinent part by J&J.

37. Among other things, the March 23, 2006 Citigroup report stated: Everolimus will likely face two IP challenges from JNJ as both its Falotico and Wright patents claim the use of a limus analogue on a stent.

38. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Citigroup analysts.

39. On January 30, 2006, Lehman Brothers published a report titled "BSX: The Risks – Part I," attached as Exhibit J ("the Lehman Brothers report"). In the Lehman Brothers report, parties are identified by their stock symbols: ABT for Abbott; GDT for Guidant; and JNJ for J&J.

40. On information and belief, the Lehman Brothers report relied on information provided in pertinent part by J&J.

41. Among other things, the Lehman Brothers report stated: There are even hypothetical litigations to contend with as JNJ has strongly suggested that they feel GDT and ABT may violate JNJ/Wyeth DES patents covering the "limus" family of drugs.

42. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Lehman Brothers analysts.

43. On March 14, 2006, Merrill Lynch published a report titled "More legal wrangling for J&J possible," attached as Exhibit K ("the Merrill Lynch report"). In the Merrill Lynch report, J&J is identified by its stock symbol JNJ.

44. On information and belief, the Merrill Lynch report relied on information provided in pertinent part by J&J.

45. Among other things, the Merrill Lynch report stated:

JNJ has two patents (Wright and Falotico) which appear to relate to the elution of characteristics of "olimus" compounds; JNJ's Cypher DES uses sirolimus, a member of the olimus family of drugs; other olimus drugs include Guidant's everolimus and Abbott/Medtronic's zotarolimus (ABT-578). The European launch of Guidant's Xience DES, which the company has targeted for Q2:06, could trigger possible legal activity since we understand U.S. patent law prohibits domestic manufacture of a product for sale outside the U.S. if there's been infringement of intellectual property.

46. On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to Merrill Lynch analysts.

47. On information and belief, J&J broadcast threatening statements to other news outlets regarding alleged infringement by XIENCE V, for publication in furtherance of J&J's public campaign.

48. ~~31.~~ On January 23, 2006, the International Herald Tribune published an article headlined "J&J works to discredit rival offer for Guidant," attached as Exhibit FL ("the International Herald article").

49. ~~32.~~ On information and belief, the International Herald article relied on information provided in pertinent part by J&J.

50. ~~33.~~ Among other things, the International Herald article stated:

"J&J is communicating to the Street that Boston Scientific's \$80-a-share offer for Guidant is fraught with uncertainty," Lawrence Biegelsen, an analyst with Prudential in New York, said in a note to clients sent on Friday.

* * *

Johnson & Johnson's campaign consists of telling analysts and shareholders that Boston Scientific is in over its head and is tempting patent litigation that may undercut Boston Scientific's plans.

"They're trying to tell all of us that there are patents out there that they have that they feel can stop Boston Scientific," said Jan David Wald, an analyst with A.G. Edwards. Wald said he had been called by a Johnson & Johnson employee, whom he declined to name.

Johnson & Johnson told analysts it was considering filing patent infringement lawsuits over stent drug coatings to keep Boston Scientific and its bidding partner, Abbott Laboratories, from profiting from the new Guidant devices, according to Biegelsen of Prudential.

* * *

Boston Scientific and J&J have been fighting in court for years over patent-infringement cases related to stent design. At the moment, the two companies are alone in the U.S. stent market, with Boston Scientific holding a 55 percent share.

* * *

The potential for Johnson & Johnson to prevent Abbott and Boston Scientific from marketing Guidant's next-generation heart stent "could give the Guidant board pause for approving a Boston Scientific-Guidant merger," Biegelsen said. "J&J claims that two of its patents may be infringed if a company tries to launch a drug-eluting stent coated with" . . . Guidant's everolimus, he wrote.

51. On January 20, 2006, the Boston Globe published an article headlined "Suitors take Guidant fight to The Street," attached as Exhibit M ("the Boston Globe article").

52. On information and belief, the Boston Globe article relied on information provided in pertinent part by I&J.

53. Among other things, the Boston Globe article stated:

[I&J] has also raised the prospect that it could use patents and existing ties to Guidant to derail or complicate Boston Scientific's offer, said Matthew Dodds, an analyst for Citigroup who is skeptical about Guidant's value to both companies.

54. Also on January 20, 2006, Crain's Chicago Business published an article headlined "Abbott stock falls on concerns over success of Guidant bid," attached as Exhibit N ("the Crain's article").

55. On information and belief, the Crain's article relied on information provided in pertinent part by I&J.

56. Among other things, the Crain's article stated:

The analyst, Prudential Equity Group, LLC's Larry Biegelsen, reported that Guidant's board could balk at Boston Scientific and Abbott's joint bid because Johnson & Johnson, a competing bidder for Guidant, claims its patents would be violated if Abbott markets its own drug-eluting stents or those made by Guidant.

57. On January 21, 2006, Reuters published an article headlined "Abbott, Boston shares off on J&I patent threat," attached as Exhibit O ("the Reuters article").

58. On information and belief, the Reuters article relied on information provided in pertinent part by J&I.

59. Among other things, the Reuters article stated:

One analyst, who asked not to be named, said J&I management was making rounds on Wall Street trying to fan fears about the Boston Scientific bid.

The analyst said J&I was arguing that Boston Scientific's bid was breaking its bank, that its assumptions on Guidant's cardiac rhythm management were too aggressive and that there was intellectual property infringement that would limit potential of important products.

60. On January 24, 2006, Medical Device Daily published an article headlined "J&I offer rumors persist as Guidant has more ICD issues," attached as Exhibit P ("the Medical Device Daily article").

61. On information and belief, the Medical Device Daily article relied on information provided in pertinent part by J&I.

62. Among other things, the Medical Device Daily article stated:

Fueling this speculation were rumors, some of which apparently were planted by J&I personnel as part of an organized campaign to undermine the Boston

Scientific offer in the minds of analysts, that two of its patents may be infringed if an unnamed company tries to launch a drug-eluting stent coated with a derivative of rapamycin.

63. On January 26, 2006, The Wall Street Journal published an article headlined "Boston Scientific Faces Pivotal Test After Victory in Fight for Guidant," attached as Exhibit Q ("the Wall Street Journal article").

64. On information and belief, the Wall Street Journal article relied on information provided in pertinent part by J&J.

65. Among other things, the Wall Street Journal article stated that: Another potential wrinkle arises in the intellectual-property rights surrounding stents -- an area that's been the subject of extensive litigation in the industry. Citigroup analyst Matthew Dodds says J&J holds patents on methods of using "limus"-type drugs on stents -- including the everolimus on Guidant's stent, as well as a drug on an Abbott stent.

66. 34.—On information and belief, J&J anticipated and intended that Abbott and others would become aware of threatening statements made by J&J to analysts and others.

67. 35.—On information and belief, J&J made additional threatening statements to industry analysts, asserting that J&J could prevent Abbott from making or selling the XIENCE V by suing for infringement of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent. On information and belief, J&J anticipated and intended that Abbott and others would become aware of these threatening statements.

68. Abbott and others did become aware of J&J's threatening statements.

69. For example, on January 20, 2006, Avram Goldstein of Bloomberg contacted Abbott regarding the Wright and Falotico patents in relation to XIENCE V.

70. On January 13, 2006, Bruce Nudell of Sanford C. Bernstein contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

71. Also on January 13, 2006, The Shaw Group contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

72. On January 20, 2006, Avram Goldstein of Bloomberg contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

73. Again on January 20, 2006, Barnaby Feder of the New York Times contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

74. On January 31, 2006, Steve Silva of Joele Frank contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

75. On March 23, 2006, Jennifer B. Pearlman of Burgundy Asset Management contacted Guidant regarding the Wright and Falotico patents in relation to XIENCE V.

76. On information and belief, in furtherance of its campaign to cast a cloud over the launch of XIENCE V, J&I made threatening statements to Guidant.

77. On January 12, 2006, J&I contacted Guidant and informed Guidant that if Boston Scientific acquired Guidant, Abbott and Boston Scientific would have problems with the Wright and Falotico patent families.

78. On January 13, 2006, J&I again contacted Guidant. J&I sent Guidant a document asserting that J&I's intellectual property portfolio included patents directed to everolimus when used on a stent. Abbott would not receive access to these patents in the event that Boston

Scientific were to acquire Guidant, and any drug eluting stent using everolimus, including XIENCE V, may infringe these patents.

79. On information and belief, J&J intended to create a substantial controversy between J&J and Abbott regarding XIENCE V's alleged infringement of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

80. 36. On information and belief, J&J intended to create the apprehension in Abbott and others that J&J would sue Abbott, following the launch of the XIENCE V, asserting that the XIENCE V allegedly infringes the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

81. 37. In March 2006, Guidant publicly announced that the XIENCE V launch would be delayed due to an issue related to manufacturing.

82. 38. As of the date of ~~this~~ the original Complaint, the XIENCE V launch ~~is~~ was imminent. On information and belief, J&J ~~is~~ was aware that the XIENCE V launch ~~is~~ was imminent and ~~is~~ was preparing to sue Abbott for infringement by the XIENCE V of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent. The XIENCE V subsequently launched in Europe.

83. 39. On information and belief, J&J has never withdrawn or retracted any of its threatening statements that, following the launch of the XIENCE V, J&J would sue Abbott for infringement of the Wright '764 patent, the Wright '536 patent, and the Falotico '796 patent.

84. On information and belief, by these statements J&J intended to create a substantial controversy between J&J and Abbott regarding alleged infringement of patents in the Wright and/or Falotico families by XIENCE V.

85. On information and belief, by these statements J&J intended to create the apprehension in Abbott and others that J&J would sue Abbott, following the launch of XIENCE V, asserting that XIENCE V allegedly infringes patents in the Wright and/or Falotico families.

J&J's Assertions In The Patent Office Of Infringement By XIENCE V

86. 40. On August 7, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the First Wright Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 10/951,385 ("Wright '385 application"). The Wright '385 application is related to the Wright '764 patent and the Wright '536 patent, and the Wright '7286 patent. On information and belief, on May 29, 2007, the Wright '385 application issued as the Wright '3286 patent. A copy of the First Wright Petition is attached as Exhibit GR.

87. 41. In the First Wright Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Wright '385 application as a patent. Among other things, counsel for J&J asserted:

Guidant's vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch the XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

* * *

I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of at least claims 103 and 130 on file in this application.

* * *

It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of at least claims 103 and 130 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

88. ~~42.~~ The subject matter of at least claim 103 of the Wright '385 application overlaps with subject matter claimed in the Wright '764 patent and the Wright '536 patent. On information and belief, claim 103 of the Wright '385 application issued on May 29, 2007 as claim 40 of the Wright '3286 patent.

89. On information and belief, the subject matter claimed in the Wright '3286 patent is not patentably distinct from subject matter claimed in at least the Wright '7286 patent, the Wright '764 patent, the Wright '536 patent, and/or United States Application Serial No. 11/466,983 ("the Wright '983 application").

90. On August 24, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the Second Wright Petition") with the United States Patent and Trademark Office in the matter of the Wright '983 application. The Wright '983 application is related to the Wright '764 patent, the Wright '536 patent, and the Wright '3286 patent. A copy of the Second Wright Petition is attached as Exhibit S.

91. In the Second Wright Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Wright '983 application as a patent. In the Second Wright Petition, J&J's counsel made assertions substantially identical to the assertions made in connection with the First Wright Petition. (See *supra* ¶ 87).

92. The subject matter of at least claim 1 of the Wright '983 application overlaps with subject matter claimed in the Wright '764 patent.

93. On information and belief, the subject matter claimed in the Wright '983 application is not patentably distinct from subject matter claimed in at least the Wright '7286 patent, the Wright '3286 patent, the Wright '764 patent, and/or the Wright '536 patent.

94. On August 24, 2006, J&J filed another "Petition to Make Special Because of Actual Infringement" ("the Third Wright Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 11/467,035 ("the Wright '035 application"). The Wright '035 application is related to the Wright '764 patent, the Wright '536 patent, and the Wright '3286 patent. On May 15, 2007, the Wright '035 application issued as the Wright '7286 patent. A copy of the Third Wright Petition is attached as Exhibit I.

95. In the Third Wright Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Wright '035 application as a patent. In the Third Wright Petition, J&J's counsel made assertions substantially identical to the assertions made in connection with the First Wright Petition. (See *supra* ¶ 87).

96. The subject matter of at least claim 1 of the Wright '7286 patent overlaps with subject matter claimed in the Wright '764 patent.

97. The subject matter claimed in the Wright '7286 patent is not patentably distinct from subject matter claimed in at least the Wright '3286 patent, the Wright '983 application, the Wright '764 patent, and/or the Wright '536 patent.

98. 43. On information and belief, J&J is preparing to assert, and has asserted, one or more patents in the Wright family, including at least the Wright '764 patent and, the Wright '536 patent, the Wright '7286 patent, and the Wright '3286 patent against the XIENCE V following its imminent launch.

99 44.—On August 7, 2006, J&J filed a “Petition to Make Special Because of Actual Infringement” (“the First Falotico Petition”) with the United States Patent and Trademark Office in the matter of United States Application Serial No. 10/829,074 (“the Falotico ’074 application”). The Falotico ’074 application is related to the Falotico ’796 patent. A copy of the First Falotico Petition is attached as Exhibit HU.

100 45.—In the First Falotico Petition, J&J asserted that it could sue Abbott for infringement by the XIENCE V immediately upon issuance of the Falotico ’074 application as a patent. Among other things, counsel for J&J asserted:

Guidant’s vascular business has recently been acquired by Abbott Laboratories (Exhibit 3). Abbott has announced that it intends to launch the XIENCE™ V in Europe in the third quarter of 2006 (Exhibit 4).

* * *

I have made a rigid comparison of the XIENCE™ V product, as described in Guidant press releases and other publicly available documents, with the claims of the instant application. In my opinion, the XIENCE™ V product is unquestionably within the scope of claims 15 to 30 on file in this application.

* * *

It is therefore my opinion that Guidant is making a product in the United States to support the European launch that is unquestionably within the scope of claims 15 to 30 of the instant application, and that a patent containing these claims could immediately be asserted upon issue.

101 46.—The subject matter of at least claim 15 of the Falotico ’074 application overlaps with subject matter claimed in the Falotico ’796 patent.

102. On August 7, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the Second Falotico Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 10/852,517 ("the Falotico '517 application"). The Falotico '517 application is related to the Falotico '796 patent. A copy of the Second Falotico Petition is attached as Exhibit V.

103. In the Second Falotico Petition, J&J asserted that it could sue Abbott for infringement by XIENCE V immediately upon issuance of the Falotico '517 application as a patent. In the Second Falotico Petition, J&J's counsel made assertions substantially identical to the assertions made in connection with the First Falotico Petition. (See supra ¶ 100).

104. The subject matter of at least claim 5 of the Falotico '517 application overlaps with subject matter claimed in the Falotico '796 patent.

105. On August 24, 2006, J&J filed a "Petition to Make Special Because of Actual Infringement" ("the Third Falotico Petition") with the United States Patent and Trademark Office in the matter of United States Application Serial No. 11/467,099 ("the Falotico '099 application"). The Falotico '099 application is related to the Falotico '796 patent. A copy of the Third Falotico Petition is attached as Exhibit W.

106. In the Third Falotico Petition, J&J asserted that it could sue Abbott for infringement by XIENCE V immediately upon issuance of the Falotico '099 application as a patent. In the Third Falotico Petition, J&J's counsel made assertions substantially identical to the assertions made in connection with the First Falotico Petition. (See supra ¶ 100).

107. The subject matter of at least claim 1 of the Falotico '099 application overlaps with subject matter claimed in the Falotico '796 patent.

108. ~~47.~~ On information and belief, J&J is preparing to assert one or more patents in the Falotico family, including at least the Falotico '796 patent, against the XIENCE V ~~following its imminent launch.~~

J&J Has Recently Sued Abbott In An Attempt To Interfere With The XIENCE V Launch

109. ~~48.~~ On September 25, 2006, J&J filed a complaint in the District Court for the Southern District of New York. Among other things, J&J alleges that Abbott Laboratories tortiously interfered with J&J's intended acquisition of Guidant. The complaint seeks no less than \$5.5 billion in damages. A copy of the complaint is attached as Exhibit ~~IX.~~

110. ~~49.~~ Although the events cited in the complaint occurred over eight months ago, J&J timed the lawsuit, on information and belief, in anticipation of the then imminent launch of XIENCE V. Both the timing of the lawsuit and the amount of the damages claimed manifest J&J's intent to cast a cloud over Abbott and interfere with the then imminent launch of the XIENCE V.

The XIENCE V Launch Is Imminent

111. ~~50.~~ As of the date of ~~this~~ the original Complaint, Abbott ~~will have had~~ manufactured, at its facilities in the United States, thousands of XIENCE V products to support its ~~imminent launch.~~

112. ~~51.~~ Abbott ~~will continue~~ has continued to manufacture XIENCE V at its facilities in the United States following the launch.

113. J&J created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Wright '764 patent, the Wright '536 patent, the Falotico '796 patent, the Wright '7286 patent, and the Wright '3286 patent by XIENCE V.

114. ~~52.~~—Abbott has a reasonable apprehension that J&J intends to sue Abbott for infringement of the Wright '764 patent, the Wright '536 patent, ~~and the Falotico '796 patent, the Wright '7286 patent, and the Wright '3286 patent,~~ by XIENCE V following its imminent launch.

CLAIM I

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 6,585,764

115. ~~53.~~—Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-~~52.~~114.

116. ~~J&J's actions have created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Wright '764 patent by XIENCE V.~~

117. ~~J&J has asserted rights under the Wright '764 patent against the XIENCE V.~~

118. ~~54.~~—J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '764 patent by XIENCE V.

119. ~~55.~~—On information and belief, the claims of the Wright '764 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

120. ~~56.~~—The XIENCE V does not infringe any valid claim of the Wright '764 patent.

121. ~~57.~~—An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '764 patent.

CLAIM II

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 6,808,536

122. ~~58.~~—Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-~~57.~~121.

123. ~~J&J's actions have created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Wright '536 patent by XIENCE V.~~

124. J&I has asserted rights under the Wright '536 patent against the XIENCE V.

125. 59. J&I's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '536 patent by XIENCE V.

126. 60. On information and belief, the claims of the Wright '536 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

127. 61. The XIENCE V does not infringe any valid claim of the Wright '536 patent.

128. 62. An actual and justiciable controversy exists between Abbott and J&I regarding invalidity and noninfringement of the Wright '536 patent.

CLAIM III

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 6,776,796

129. 63. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-62. 128.

130. J&I's actions have created a substantial controversy between J&I and Abbott regarding the alleged infringement of the Falotico '796 patent by XIENCE V.

131. J&I has asserted rights under the Falotico '796 patent against the XIENCE V.

132. 64. J&I's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Falotico '796 patent by XIENCE V.

133. 65. On information and belief, the claims of the Falotico '796 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

134. 66. The XIENCE V does not infringe any valid claim of the Falotico '796 patent.

135. 67.—An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Falotico '796 patent.

CLAIM IV

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 7,217,286

136. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-135.

137. The Wright '7286 patent issued on May 15, 2007.

138. J&J's actions have created a substantial controversy between J&J and Abbott regarding the alleged infringement of the Wright '7286 patent by XIENCE V.

139. J&J has asserted rights under the Wright '7286 patent against the XIENCE V.

140. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '7286 patent by XIENCE V.

141. On information and belief, the claims of the Wright '7286 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103, and 112.

142. The XIENCE V does not infringe any valid claim of the Wright '7286 patent.

143. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '7286 patent.

CLAIM V

INVALIDITY AND NONINFRINGEMENT OF U.S. PATENT NO. 7,223,286

144. Abbott realleges and incorporates by reference the allegations set forth in paragraphs 1-143.

145. On information and belief, the Wright '3286 patent issued on May 29, 2007.

146. J&J's actions have created a substantial controversy between J&J and Abbott regarding alleged infringement of the Wright '3286 patent by XIENCE V.

147. J&J has asserted rights under the Wright '3286 patent against the XIENCE V.

148. J&J's actions have placed Abbott in reasonable apprehension that it will be sued for infringement of the Wright '3286 patent by XIENCE V.

149. On information and belief, the claims of the Wright '3286 patent are invalid for failure to meet the requirements for patentability, including the requirements of 35 U.S.C. §§ 102, 103 and 112.

150. The XIENCE V does not infringe any valid claim of the Wright '3286 patent.

151. An actual and justiciable controversy exists between Abbott and J&J regarding invalidity and noninfringement of the Wright '3286 patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request entry of judgment in their favor that:

(a) each and every claim of U.S. Patent No. 6,585,764 is invalid;

(b) each and every claim of U.S. Patent No. 6,808,536 is invalid;

(c) each and every claim of U.S. Patent No. 6,776,796 is invalid;

(d) each and every claim of U.S. Patent No. 7,217,286 is invalid;

(e) each and every claim of U.S. Patent No. 7,223,286 is invalid;

(f) ~~(d)~~ Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 6,585,764;

(g) ~~(e)~~ Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 6,808,536;

(h) ~~(f)~~ Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 6,776,796;

(i) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 7,217,286;

(j) Plaintiffs are not liable for any infringement, for any contributory infringement, or for inducing the infringement of U.S. Patent No. 7,223,286;

(k) ~~(g)~~ Defendants and their officers, agents, employees, representatives, counsel and all persons in active concert or participation with any of them, directly or indirectly, be enjoined from threatening or charging infringement of, or instituting any action for infringement of any of U.S. Patent Nos. 6,585,764, 6,808,536, and ~~6,776,796~~ 6,776,796, 7,217,286, and 7,223,286 against Plaintiffs, their suppliers, customers, distributors or users of their products;

(l) ~~(h)~~ Defendants pay to Plaintiffs the costs and reasonable attorneys fees incurred by Plaintiffs in this action; and

(m) ~~(i)~~ Plaintiffs be granted such other and further relief as this Court deems just and proper.

JURY TRIAL DEMANDED

Plaintiffs demand a trial by jury on all issues so triable.

OF COUNSEL:

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ATTORNEYS FOR PLAINTIFFS ABBOTT
LABORATORIES and ~~ADVANCED ABBOTT~~
CARDIOVASCULAR SYSTEMS, INC.

Date: ~~September~~ May 29, 2006 2007

EXHIBIT 3



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/951,385	09/28/2004	Carol Wright	JJI-51-CON2	7537
45511	7590	11/20/2006	EXAMINER	
WOODCOCK WASHBURN LLP CIRA CENTRE, 12TH FLOOR 2929 ARCH STREET PHILADELPHIA, PA 19104-2891			GHERBI, SUZETTE JAIME J	
			ART UNIT	PAPER NUMBER
			3738	

DATE MAILED: 11/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/951,385	WRIGHT ET AL.	
	Examiner	Art Unit	
	Suzette J. Gherbi	3738	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 28 September 2004.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 64-140 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 64-140 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some * c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08)

Paper No(s)/Mail Date 8/7/04; 12/5/05.

4) ☐ Interview Summary (PTO-413)

Paper No(s)/Mail Date: _____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

Application/Control Number: 10/951,385
Art Unit: 3738

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DETAILED ACTION

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

ABT 007923

Application/Control Number: 10/951,385
Art Unit: 3738

Page 3

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 64-140 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,585,764. Although the conflicting claims are not identical, they are not patentably distinct from each other because it is obvious to one having ordinary skill in the art that the current patent application merely rewords the claimed structure and it is also obvious that it is biocompatible.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzette J-J Gherbi whose work schedule is Maxi-Flex off every other Friday and whose telephone number is 571-272-4751.

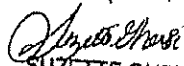
The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0858.

Application/Control Number: 10/951,385
Art Unit: 3738

Page 4

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


SUZETTE GHERBI
PRIMARY EXAMINER
TECHNOLOGY CENTER 3700
13 November 2006

DOCKET NO.: CRDS-0005 (JJ1-51-CON2)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Carol Wright, et al.

Confirmation No.: 7537

Application No.: 10/951,385

Group Art Unit: 3738

Filing Date: September 28, 2004

Examiner: Suzette J.J. Gherbi

For: Local Delivery of Rapamycin for Treatment of Proliferative Sequelae
Associated with PTCA Procedures, Including Delivery Using a Modified
Stent

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL
DOUBLE PATENTING REJECTION OF A PENDING APPLICATION

The owner, **Cordis Corporation**, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173 as shortened by any terminal disclaimer filed prior to the grant of any patent granted on pending Application Number 11/466,983 and Application Number 11/467,035, both filed on **August 24, 2006**. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on these applications are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of any patent granted on Application Number 11/466,983 and Application Number 11/467,035, as shortened by any

ABT 007908

DOCKET NO.:CRDS-0005 (JJ1-51-CON2) - 2 -

PATENT

terminal disclaimer filed prior to the patent grant, in the event that any such granted patent: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR § 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

☒ The undersigned is an attorney of record.

Date: January 3, 2007

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
Cira Centre
2929 Arch Street, 12th Floor
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

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DOCKET NO.: CRDS-0005 (JJ1-51-CON2)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Carol Wright, et al.

Confirmation No.: 7537

Application No.: 10/951,385

Group Art Unit: 3738

Filing Date: September 28, 2004

Examiner: Suzette J.J. Gherbi

For: Local Delivery of Rapamycin for Treatment of Proliferative Sequelae Associated with PTCA Procedures, Including Delivery Using a Modified Stent

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE
PATENTING REJECTION OVER A PRIOR PATENT

The owner, Cordis Corporation, of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent Nos. 6,273,913, 6,585,764, and 6,808,536. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the said prior patents are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the said prior patents, as presently shortened by any terminal disclaimer, in the event that any of said patents: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37

ABT 007910

DOCKET NO.: CRDS-0005

- 2 -

PATENT

CFR § 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

☒ The undersigned is an attorney of record.

Date: January 3, 2007

/S. Maurice Valla/
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Registration No. 43,966

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ABT 007911

Abbott Laboratories and Advanced Cardiovascular Systems, Inc v Johnson and
Johnson, Inc and Cordis Corporation DEDC C A No. 06-613-SLR

EXHIBIT 4



UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/466.983	06/12/2007	7229473	CRDS-0066	2883

45511 7590 05/23/2007
 WOODCOCK WASHBURN LLP
 CIRA CENTRE, 12TH FLOOR
 2929 ARCH STREET
 PHILADELPHIA, PA 19104-2891

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
 (application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

Robert Falotico, Bell Mead, NJ;
 Gerard H. Llanos, Stewartville, NJ;



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY DOCKET NO	TOT CLAIMS	IND CLAIMS
11/466,983	08/24/2006	3738	1660	CRDS-0066	5	1

CONFIRMATION NO. 2883

CORRECTED FILING RECEIPT

45511
 WOODCOCK WASHBURN LLP
 CIRA CENTRE, 12TH FLOOR
 2929 ARCH STREET
 PHILADELPHIA, PA 19104-2891

Date Mailed: 05/17/2007

Receipt is acknowledged of this regular Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please mail to the Commissioner for Patents P.O. Box 1450 Alexandria Va 22313-1450. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Robert Falotico, Bell Mead, NJ;
 Gerard H. Llanos, Stewartsville, NJ;

Assignment For Published Patent Application

Cordis Corporation, Miami Lakes, FL

Power of Attorney: The patent practitioners associated with Customer Number 45511

Domestic Priority data as claimed by applicant

This application is a CON of 10/951,385 09/28/2004 PAT 7,223,286
 which is a CON of 10/408,328 04/07/2003 PAT 6,808,536
 which is a CON of 09/874,117 06/04/2001 PAT 6,585,764
 which is a CON of 09/061,568 04/16/1998 PAT 6,273,913
 which claims benefit of 60/044,692 04/18/1997

Foreign Applications

If Required, Foreign Filing License Granted: 09/05/2006

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is
US11/466,983

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE
SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY
USING A MODIFIED STENT

Preliminary Class

623

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier

license of similar scope has been granted under 37 CFR 5.13 or 5.14

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).